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L4 ANSWER 1 OF 17 CAPLUS COPYRIGHT 2004 ACS on STN
2004:610096 Document No. 141:156082 Methods for use of Notch signaling for modulation of cytokine production in T cells and therapeutic uses thereof. Champion, Brian Robert; Young, Lesley Lynn; McKenzie, Grahame James (Lorantis Limited, UK). PCT Int. Appl. WO 2004062686 A2 20040729, 149 pp. DESIGNATED STATES: W: AE, AE, AG, AL, AL, AM, AM, AM, AT, AT, AU, AU, AZ, AZ, BA, BB, BG, BG, BR, BR, BW, BY, BY, BZ, BZ, CA, CH, CN, CN, CO, CO, CR, CR, CU, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EC, EE, EE, EG, ES, ES, FI, FI, GB, GD, GE, GE, GH, GH, GH, GM, HR, HR, HU, HU, ID, IL, IN, IS, JP, JP, KE, KE, KG, KG, KP, KP, KP, KR, KR, KZ, KZ, KZ, LC, LK, LR, LS, LS, LT, LU, LV, MA, MD, MD, MG, MK, MN, MW, MX, MX, MZ. (English). CODEN: PIXXD2. APPLICATION: WO 2004-GB21 20040109. PRIORITY: GB 2003-428 20030109.

AB The invention provides methods for use of modulators of Notch signaling to regulate interleukin 4 expression and T cell immune responses. The invention further claims use of the methods for immunotherapy, to modify the TH1/TH2 balance of an immune response in favor of a TH2 response, by treatment of patient's cells in vivo or **ex vivo**. In the examples of the invention, a fusion protein comprising the extracellular domain of human Delta1 ligand fused to the Fc domain of human IgG4 was immobilized in microtiter plates via its Fc domain. CD4-pos. cell were cultured in the presence of the above fusion protein, stimulated with anti-CD28 antibody, and analyzed for cDNA expression by PCR. The CD4+ cells were restimulated in various ways and the cytokines IL-10 and interferon-γ were measured. Notch ligand signaling was also measured using a luciferase reporter construct in CHO cells cocultured with recombinant CHO cells expressing Delta1 ligand on the surface. Cytokine production was measured in stimulated mouse CD4+ cells under polarizing conditions. Transcription factor and cytokine expression by anti-CD3/28 activated mouse T cells activated under neutral, Th1, or Th2 culture conditions was measured with or without Delta1 protein.

L4 ANSWER 2 OF 17 CAPLUS COPYRIGHT 2004 ACS on STN
2003:991374 Document No. 140:40879 Bifunctional CpG or oligo-/polynucleotide and toxin or enterotoxin containing composition. Holmgren, Jan; Harandi, Ali M. (Gotovax AB, Swed.). PCT Int. Appl. WO 2003103708 A1 20031218, 46 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO

2003-SE935 20030605. PRIORITY: SE 2002-1701 20020605; US 2002-PV385588 20020605.

AB A bifunctional composition comprising an intracellularly effective immunomodulating nucleic acid component containing at least one immunostimulatory, immunoinhibitory, or immunomodulating motif and selected from a mononucleotide, a dinucleotide, an oligonucleotide or a polynucleotide with either a natural phosphodiester backbone or a modified backbone, optionally in combination with a specific antigen, in association with a protein binding to specific receptors on mammalian cell surfaces selected from the group consisting of cholera toxin (CT), the subunit B of CT (CTB), Escherichia coli heat-labile enterotoxin (LT), the subunit B of LT (LTB), and proteins or protein derivs. that react with antiserum to CT or LT, bind to GM1 ganglioside, ADP-ribosylates an acceptor protein, or give rise to accumulation of cAMP in target cells, and antibodies or other proteins which after binding to a specific cell surface component can be internalized into the cell, is described. The composition is useful for treatment of tumors, infections, graft rejections, immunosuppressive states, autoimmune diseases and **allergies**, and further with a specific antigen it is useful for immunoprophylaxis, immunotherapy or induction of tolerance, and for treatment **ex vivo** of an **antigen-presenting cell** for subsequent infusion into a mammal for vaccination or immunotherapy purposes.

L4 ANSWER 3 OF 17 CAPLUS COPYRIGHT 2004 ACS on STN

2002:951502 Document No. 138:54130 Modulation of the T Cell Response to β-Lactoglobulin by Conjugation with Carboxymethyl Dextran. Kobayashi, Kazuo; Yoshida, Tadashi; Takahashi, Koji; Hattori, Makoto (Department of Applied Biological Science, Faculty of Agriculture, Tokyo University of Agriculture and Technology, Tokyo, Japan). Bioconjugate Chemistry, 14(1), 168-176 (English) 2003. CODEN: BCCHES. ISSN: 1043-1802. Publisher: American Chemical Society.

AB The authors have previously prepared β-lactoglobulin (β-LG)-carboxymethyl dextran (CMD) conjugates with water-soluble carbodiimide and achieved reduced immunogenicity of β-LG. In the present study, to elucidate the mechanism for the reduced immunogenicity of β-LG, the authors investigated changes in the T cell response to β-LG after conjugation with CMDs differing in mol. weight (about 40 and 162 kDa). Lymph node cells from BALB/c, C3H/He, and C57BL/6 mice that had been immunized with β-LG or the conjugates were stimulated with β-LG, and the in vivo T cell response was then evaluated by BrdU (5-bromo-2'-deoxyuridine) ELISA as the **ex vivo** proliferative response. T cells from the conjugate-immunized mice showed a lower proliferative response than those from the β-LG-immunized mice. T cell epitope scanning, using synthesized peptides, showed that the T cell epitope profiles of the conjugates were similar to those of β-LG, whereas the proliferative response to each epitope was reduced. These results indicate that the lower in vivo T cell response with the conjugates was not due to induction of conjugate-specific T cells, but due to a decrease in the number of β-LG-specific T cells. After the lymph node cells from β-LG-immunized mice had been stimulated with β-LG or the conjugates, the efficiency of the antigen presentation of the conjugate to β-LG-specific T cells was evaluated by BrdU ELISA as the in vitro proliferative response. The antigen presentation of β-LG to the T cells was reduced by conjugation with CMD. In addition, conjugation with CMD enhanced the resistance of β-LG to cathepsin B and cathepsin D, which suggest that conjugation with CMD inhibited the degradation of β-LG by proteases in APC and led to suppression of the generation of antigenic peptides including T cell epitopes from β-LG. It is therefore considered that the suppressive effect on the generation of T cell epitopes reduced the antigen presentation of the conjugates and that this reduction led to a decrease in the number of β-LG-specific T cells in vivo. As a result, the decreased help to B cells by T cells would have reduced the antibody response to β-LG. The authors conclude that suppression of the generation of T cell epitopes by conjugation with CMD is important to the mechanism for the reduced immunogenicity of β-LG.

L4 ANSWER 4 OF 17 CAPLUS COPYRIGHT 2004 ACS on STN
2003:513565 Document No. 139:132148 Intranodal injection of semimature monocyte-derived dendritic cells induces T helper type 1 responses to protein neoantigen. Gilliet, Michel; Kleinhans, Martin; Lantelme, Erica; Schadendorf, Dirk; Burg, Guenter; Nestle, Frank O. (Department of Dermatology, University of Zurich Medical School, Zurich, Switz.). Blood, 102(1), 36-42 (English) 2003. CODEN: BLOOAW. ISSN: 0006-4971. Publisher: American Society of Hematology.

AB Dendritic cells (DCs) represent the most potent **antigen-presenting cells** of the immune system capable of initiating primary immune responses to neoantigens. Here the authors characterize the primary CD4 T-cell immune response to protein keyhole limpet hemocyanin (KLH) in 5 metastatic melanoma patients undergoing a tumor peptide-based dendritic cell vaccination trial. Monocyte-derived dendritic cells displaying a semimature phenotype, as defined by surface markers, were loaded **ex vivo** with antigen and injected intranodally at weekly intervals for 4 wk. All patients developed a strong and long-lasting delayed-type hypersensitivity reactivity to KLH, which correlated with the induction of KLH-dependent proliferation of CD4 T cells in vitro. Secondary in vitro stimulation with KLH showed significant increase in interferon-γ and interleukin-2 (IL-2) but not IL-4, IL-5, nor IL-10 secretion by bulk T cells. On the single-cell level, most TH1 cells among in vitro-generated KLH-specific T-cell lines confirmed the preferential induction of a KLH-specific type 1 T helper immune response. Furthermore, the induction of KLH-specific antibodies of the IgG2 subtype may reflect the induction of a type 1 cytokine profile in vivo after vaccination. The authors' results indicate that intranodal vaccination with semimature DCs can prime strong, long-lasting CD4 T-cell responses with a TH1-type cytokine profile in cancer patients.

L4 ANSWER 5 OF 17 CAPLUS COPYRIGHT 2004 ACS on STN
2002:888894 Document No. 138:3652 **Ex-vivo** priming for generating cytotoxic T lymphocytes specific for non-tumor self antigens to treat autoimmune and allergic disease. Cai, Zeling; Jackson, Michael R.; Peterson, Per A.; Shi, Weixing; Kong, Yan; Degraw, Juli (Ortho-McNeil Pharmaceutical, Inc., USA). PCT Int. Appl. WO 2002092773 A2 20021121, 97 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-US15341 20020513. PRIORITY: US 2001-PV291300 20010515.

AB Cytotoxic T lymphocytes (CTLs) specific for antigenic peptides derived from IgE mol. can be generated in vitro by stimulating resting naive CD8 T celles with IgE peptides presented by artificial **antigen presenting cells.** The IgE specific CTLs lyse the target cells loaded with IgE peptides in vitro and inhibit antigen specific IgE response in vivo. In addition, adoptive transfer of the IgE specific CTL to an asthmatic mouse model can inhibit the development of lung inflammation and airway hypersensitivity. IgE specific CTL provides a treatment for allergic asthma and other IgE-mediated allergic diseases. Antigenic peptides identified from non-tumor self-antigens induce specific cytotoxic T lymphocyte (CTL) in vitro. The CTL induced by peptides identified from CD40L can kill activated CD4 T cells. In vitro generated CTL specific for CD40L inhibit CD4-dependent antibody responses of all isotypes in vivo. In contrast, CTL induced by antigenic peptides derived from IgE specifically inhibit IgE responses, and adoptive transfer of CD40L-specific CTL to NOD mice at early age delay the adoptive transfer of CD40L-specific CTL to NOD mice at early age delay the development of diabetes in NOD mice. In vitro generated CTl specific for non-tumor self-antigens expressed on activated CD4 T cells regulate immune responses

in vivo.

L4 ANSWER 6 OF 17 MEDLINE on STN DUPLICATE 1
2002698500. PubMed ID: 12459166. Quantitative analysis of the antigen-specific IFNgamma+ T cell-mediated immune response in conventional outbred pigs: kinetics and duration of the DNA-induced IFNgamma+ CD8+ T cell response. Laval F; Paillot R; Bollard S; Fischer L; Audonnet J-C; Andreoni C; Juillard V. (Discovery Research, Merial, 254 Rue Marcel Merieux, BP 7009, 63342 Lyon Cedex 07, France.) Veterinary immunology and immunopathology, (2002 Dec) 90 (3-4) 191-201. Journal code: 8002006. ISSN: 0165-2427. Pub. country: Netherlands. Language: English.

AB It is now well established that antigen-specific CD8(+) T cells play a major role in vaccine-induced immunity against intracellular pathogens and tumor cells. The detection of these immune cells in outbred animals has been hampered mainly by the need to generate individual autologous **antigen-presenting cells** (APCs) due to the high degree of polymorphism of the major histocompatibility complex (MHC) Class I loci. We used individually derived immature porcine dendritic cells infected with a pox-based recombinant viral vector to **ex vivo** stimulate PBMCs from vaccinated conventional pigs. The frequencies of antigen-specific T cells was determined by the number of IFNgamma-secreting cells in a quantitative enzyme-linked immune spot (ELISPOT) assay. Using this approach we were able to rank different pseudorabies virus (PRV) vaccines strategies for their ability to prime viral-specific IFNgamma(+) T cells. Plasmid DNA has recently emerged as a promising tool with multiple applications in the field of infectious diseases, **allergy** and cancer. We showed for the first time in this study that DNA immunization induced a long-lived antigen-specific IFNgamma(+) T cells response in conventional pigs. Additional studies allowed us to show that these virus-specific IFNgamma(+) responding cells detected in this ELISPOT assay were MHC-restricted and comprised in the CD8alpha(bright) pig T cell subset. These new data confirm the usefulness of DNA vaccines to control diseases requiring cellular immunity in pigs. Copyright 2002 Elsevier Science B.V.

L4 ANSWER 7 OF 17 CAPLUS COPYRIGHT 2004 ACS on STN
2001:935657 Document No. 136:68708 Monoclonal and polyclonal antibodies specific for invariant TCR+ T cell subpopulations. Exley, Mark A.; Wilson, Samuel B.; Balk, Steven P. (Beth Israel Deaconess Medical Center, USA; Dana-Farber Cancer Institute, Inc.). PCT Int. Appl. WO 2001098357 A2 20011227, 151 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US19670 20010619. PRIORITY: US 2000-PV212466 20000619.

AB The authors disclose antibodies for the **ex vivo** or in vivo activation and expansion of NK T cells, CD1d-reactive T cells, and JαQ+ cells and the modulation of their activities. In one example, monoclonal antibodies to the CDR3 region of human invariant TCR α-chain were prepared by immunization of CD1d-knockout mice with a cyclic peptide. Application of these antibodies to human prostate cancer patients demonstrated a depression in levels and function of NK T-cells.

L4 ANSWER 8 OF 17 MEDLINE on STN DUPLICATE 2
2001490819. PubMed ID: 11533211. Adeno-associated virus type 2-mediated transduction of human monocyte-derived dendritic cells: implications for **ex vivo** immunotherapy. Ponnazhagan S; Mahendra G; Curiel D T; Shaw D R. (Department of Pathology, University of Alabama at Birmingham, 35294-0007, USA.. sponnazh@path.uab.edu) . Journal of virology, (2001 Oct) 75 (19) 9493-501. Journal code: 0113724. ISSN:

0022-538X. Pub. country: United States. Language: English.

AB Dendritic cells (DCs) are pivotal **antigen-presenting cells** for regulating immune responses. A major focus of contemporary vaccine research is the genetic modification of DCs to express antigens or immunomodulatory molecules, utilizing a variety of viral and nonviral vectors, to induce antigen-specific immune responses that ameliorate disease states as diverse as malignancy, infection, autoimmunity, and **allergy.** The present study has evaluated adeno-associated virus (AAV) type 2 as a vector for **ex vivo** gene transfer to human peripheral blood monocyte (MO)-derived DCs. AAV is a nonpathogenic parvovirus that infects a wide variety of human cell lineages in vivo and in vitro, for long-term transgene expression without requirements for cell proliferation. The presented data demonstrate that recombinant AAV (rAAV) can efficiently transduce MOs as well as DCs generated by MO culture with granulocyte-macrophage colony-stimulating factor plus interleukin in vitro. rAAV transgene expression in MO-derived DCs could be enhanced by etoposide, previously reported to enhance AAV gene expression. rAAV transduction of freshly purified MO followed by 7 days of culture with cytokines to generate DCs, and subsequent sorting for coexpression of DC markers CD1a and CD40, showed robust transgene expression as well as evidence of nuclear localization of the rAAV genome in the DC population. Phenotypic analyses using multiple markers and functional assays of one-way allogeneic mixed leukocyte reactions indicated that rAAV-transduced MO-derived DCs were as equivalent to nontransduced DCs. These results support the utility of rAAV vectors for future human DC vaccine studies.

L4 ANSWER 9 OF 17 CAPLUS COPYRIGHT 2004 ACS on STN

2000:191190 Document No. 132:235912 **Antigen-presenting cells** and their use in therapy. Wauben, Marc Henriette Michaela; Van Eden, Willem (Upither B. V., Neth.). PCT Int. Appl. WO 2000015767 A2 20000323, 25 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-NL575 19990915. PRIORITY: EP 1998-203083 19980915.

AB A method for **ex vivo** treatment of **antigen presenting cells**, wherein said method consists of in vitro culture of **antigen presenting cells** under conditions resulting in development of tolerogenic **antigen presenting cells**, such tolerogenic cells being characterized by: (a) reduced induction of T cell activation upon T-cell receptor ligation as can be determined by any of the measurements selected from the group measurement of proliferation, measurement of cytokine production, measurement of cytotoxicity and measurement of expression of activation cell surface markers, (b) a dominant tolerogenic effect. Also part of the invention are such tolerogenic **antigen-presenting cells** and artificial analogs, compns. containing them and their use in immunotherapy.

L4 ANSWER 10 OF 17 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

2000309482 EMBASE The effect of VAS972 on allergic contact hypersensitivity. Shivji G.M.; Suzuki H.; Mandel A.Sh.; Bolton A.E.; Sauder D.N.. Dr. D.N. Sauder, Division of Dermatology, Sunnybrook and Women's College, Health Science Centre, 2075 Bayview Ave, Toronto, Ont. M4N 3M5, Canada. Journal of Cutaneous Medicine and Surgery 4/3 (132-137) 2000.
Refs: 28.
ISSN: 1203-4754. CODEN: JCMSFU. Pub. Country: Canada. Language: English.
Summary Language: English; French.

AB Background: Contact hypersensitivity (CHS) is a Th1-mediated immune

response that can be down-regulated by immunosuppressive agents such as cyclosporine and environmental stimuli such as ultraviolet light. Recently, an immunomodulation therapy, VAS972, has been developed which is believed to down-regulate the Th1 arm of the immune response. This VAS972 involves modifying autologous blood by controlled exposure to the oxidizing agent ozone and UVC light, at an elevated temperature **ex vivo**. The processed blood is then administered by intramuscular injection. Objective: To further evaluate the immune modulating effect of VAS972. Methods: We examined the effect of VAS972 treatment on CHS. Contact hypersensitivity was induced with dinitrofluorobenzene (DNFB) in animals receiving VAS972-processed blood, control blood, or saline. A preliminary study was also conducted to evaluate the effect of plasma and cellular fractions of processed blood. Results: Mice injected with VAS972-processed blood demonstrated a significantly lower (46%) CHS response than controls. Histologic examination of challenged ear skin from control mice displayed edema with a significant lymphocytic infiltration, whereas animals administered processed blood demonstrated a reduction in lymphocytic infiltration. Mice injected with either plasma or the cellular fraction of the VAS972-treated blood also demonstrated a significant suppression (49% and 41%, respectively). Conclusion: The results of this study demonstrated that VAS972 suppresses CHS and cellular infiltration. Furthermore, the plasma and cellular components of the VAS972 treatment were also able to induce immunosuppression. This further supports the hypothesis that VAS972 down-regulates the Th1 arm of the immune response.

L4 ANSWER 11 OF 17 CAPLUS COPYRIGHT 2004 ACS on STN
1999:635440 Document No. 131:270966 Engineered **antigen presenting cells** and methods for their use. Robinson, William S. (Leland Stanford Junior University, USA). U.S. US 5962320 A 19991005, 13 pp. (English). CODEN: USXXAM. APPLICATION: US 1997-888360 19970703.

AB Autologous, heterologous or xenogeneic primary cells or cell lines are genetically modified **ex vivo** to render the cells capable of processing and presenting selected antigens to cells of the immune system of a subject, and to express different HLA mols. for matching to the HLA specificity of the subject. The cells are also modified to express immunoregulatory mols. for directing the immune response of the subject. The cells and cell lines are used in methods to treat infectious diseases or cancer, or to prevent infectious disease by inoculation into a host to activate T cells and induce an antigen-specific immune response, and in assays of the cytolytic activity of a subject's T cells. The cells can also be used to suppress an unwanted immune response of a subject to a selected antigen where the cells lack expression of a costimulation mol. needed for T cell activation.

L4 ANSWER 12 OF 17 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
1999019596 EMBASE UVA-induced immune suppression through an oxidative pathway. Iwai I.; Hatao M.; Naganuma M.; Kumano Y.; Ichihashi M.. Dr. M. Hatao, Nippa-cho, Kohoku-ku, Yokohama 223, Japan. Journal of Investigative Dermatology 112/1 (19-24) 1999.
Refs: 48.
ISSN: 0022-202X. CODEN: JIDEAE. Pub. Country: United States. Language: English. Summary Language: English.

AB Although ultraviolet B (UVB) irradiation induces local immune or systemic immune suppression, depending on the dose, the immune suppression by ultraviolet A (UVA) has not been fully investigated. In this study, we investigated the effect of UVA on the immune response in vitro and in vivo. The effect of UVA on the antigen-presenting function of epidermal cells was measured in terms of antigen-specific T cell proliferation. A murine epidermal cell suspension was exposed to UVA in vitro, pulsed with trinitrobenzenesulfonic acid, and cultured with T cells prepared from syngeneic mice previously sensitized with trinitrochlorobenzene. UVA (5-20 J per cm2) suppressed the antigen-presenting function of epidermal cells in a dose-dependent manner, accompanied with suppression of the expression

of costimulatory molecules on Langerhans cells. In order to investigate the effect of an antioxidant on the immune suppression, an epidermal cell suspension was irradiated with UVA in the presence or absence of glutathione. The suppressions of antigen-presenting function and ICAM-1 expression were significantly prevented by glutathione in a dose-dependent manner. Further, the effect of UVA on the immune response at the induction phase of contact hypersensitivity was evaluated in terms of lymph node cell proliferation **ex vivo.** UVA irradiation suppressed the endogenous proliferation of lymph node cells in trinitrochlorobenzene-painted mice, and this suppression was significantly reversed by the application of glutathione to the skin during irradiation. These results suggest that UVA-induced immune suppression may be mediated by reactive oxygen species, at least in part.

L4 ANSWER 13 OF 17 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN

1998:257468 Document No.: PREV199800257468. Effects of peptide therapy on **ex vivo** T-cell responses. Marcotte, Gregory V.; Braun, Christine M.; Norman, Philip S.; Nicodemus, Christopher E.; Kagey-Sobotka, Anne; Lichtenstein, Lawrence M.; Essayan, David M. [Reprint author]. Johns Hopkins Asthma Allergy Center, 5501 Hopkins Bayview Circle, Baltimore, MD 21224, USA. Journal of Allergy and Clinical Immunology, (April, 1998) Vol. 10, No. 4 PART 1, pp. 506-513. print.
CODEN: JACIBY. ISSN: 0091-6749. Language: English.

AB Background: Peptide therapy targets T cells directly with short peptides containing multiple T-cell receptor epitopes. Murine studies suggest T-cell anergy as the mechanism of action; however, changes in T-cell cytokine profiles may be more relevant in human beings. Objective: We sought to study the effects of peptide therapy on **ex vivo** antigen-specific T-cell responses. Methods: Antigen-specific T-cell lines were generated from subjects enrolled in a double-blind, placebo controlled, two-dose study of the ALLERVAX CAT therapeutic, containing Fel d 1 peptides (ImmuLogic Pharmaceutical Corp., Waltham, Mass.) (n=7, 8, and 7, respectively, for groups receiving placebo, 75 mug, or 750 mug). Each subject had three lines propagated before and after receiving peptide therapy; antigens used were cat hair extract, Fel d 1 peptides, and tetanus toxoid (negative control). Proliferative responses and cytokine generation from each line were assessed after two restimulations with antigen and autologous **antigen-presenting cells.** Results: The Fel d 1 peptide lines showed a dose-dependent decrease of IL-4 production ($p=0.02$ and 0.025, respectively, for the 750 Kg group vs both the 75 mug and placebo groups). IL-4 production from the cat hair allergen extract lines and interferon-gamma production from both the Fel d 1 peptide lines and cat hair allergen extract lines showed no statistically significant changes. The control tetanus toxoid lines showed no changes in cytokine production; there were no significant changes in proliferation with any of the antigens in any of the treatment groups. In the clinical arm of the trial, only the 750 mug dose of peptides produced a significant response. Conclusions: Peptide therapy induces a significant, dose-dependent decrease in peptide-stimulated IL-4 production, consistent with either a shift in T-cell phenotype or peptide-specific T-cell tolerance.

L4 ANSWER 14 OF 17 CAPLUS COPYRIGHT 2004 ACS on STN

1998:280991 Document No. 129:103924 Effects of peptide therapy on **ex vivo** T-cell responses. Marcotte, Gregory V.; Braun, Christine M.; Norman, Philip S.; Nicodemus, Christopher F.; Kagey-Sobotka, Anne; Lichtenstein, Lawrence M.; Essayan, David M. (The Division of Clinical Immunology, Johns Hopkins University School of Medicine, Baltimore, MD, USA). Journal of Allergy and Clinical Immunology, 101(4, Pt. 1), 506-513 (English) 1998. CODEN: JACIBY. ISSN: 0091-6749. Publisher: Mosby, Inc..

AB Peptide therapy targets T cells directly with short peptides containing multiple T-cell receptor epitopes. Murine studies suggest T-cell anergy as the mechanism of action; however, changes in T-cell cytokine profiles may be more relevant in human beings. We sought to study the effects of

peptide therapy on **ex vivo** antigen-specific T-cell responses. Antigen-specific T-cell lines were generated from subjects enrolled in a double-blind, placebo controlled, two-dose study of the ALLERVAX CAT therapeutic, containing Fel d 1 peptides (ImmuLogic Pharmaceutical Corp., Waltham, Mass.) (n = 7,8, and 7, resp., for groups receiving placebo, 75 μg, or 750 μg). Each subject had three lines propagated before and after receiving peptide therapy; antigens used were cat hair extract, Fel d 1 peptides, and tetanus toxoid (neg. control). Proliferative responses and cytokine generation from each line were assessed after two re-stimulations with antigen and autologous **antigen-presenting cells.** The Fel d 1 peptide lines showed a dose-dependent decrease of IL-4 production ($p = 0.02$ and 0.025, resp., for the 750 μg group vs both the 75 μg and placebo groups). IL-4 production from the cat hair allergen extract lines and interferon-γ production from both the Fel d 1 peptide lines and cat hair allergen extract lines showed no statistically significant changes. The control tetanus toxoid lines showed no changes in cytokine production; there were no significant changes in proliferation with any of the antigens in any of the treatment groups. In the clin. arm of the trial, only the 750 μg dose of peptides produced a significant response. Peptide therapy induces a significant, dose-dependent decrease in peptide-stimulated IL-4 production, consistent with either a shift in T-cell phenotype or peptide-specific T-cell tolerance.

L4 ANSWER 15 OF 17 MEDLINE on STN DUPLICATE 3

1998230256. PubMed ID: 9570330. A modified murine local lymph node assay for the differentiation of contact photoallergy from phototoxicity by analysis of cytokine expression in skin-draining lymph node cells. Ulrich P; Homey B; Vohr H W. (Experimental Toxicology, Novartis Pharma AG, Basel, Switzerland.. peter.ulrich@pharma.novartis.com) . Toxicology, (1998 Feb 6) 125 (2-3) 149-68. Journal code: 0361055. ISSN: 0300-483X. Pub. country: Ireland. Language: English.

AB Since predictive differentiation of photoallergenic from phototoxic reactions, induced by low molecular weight compounds, represents a current problem, we tried to improve the differentiation between the two reactions by using a modified protocol of the local lymph node assay (LLNA). Briefly, groups of female BALB/c mice received compound solution or vehicle alone on the dorsum of both ears on 3 consecutive days. Immediately after compound application indicated groups of mice were exposed to a UVA light-dose of 10 J/cm2. Auricular lymph nodes draining the ear tissue were excised 24 h following the last exposure. Evaluation consisted of assessing lymph node weights and cell counts to monitor organ hyperplasia and in vivo-proliferative events following substance application. Furthermore, we analysed cytokine gene transcription in freshly prepared lymph node cells (LNC) and the cytokine release in vitro by restimulated CD4+ T-cells and **antigen presenting cells** (APC), both purified from the skin-draining lymph nodes. Both contact (photo) allergenic (oxazolone and tetrachlorosalicylanilide) and phototoxic substances (8-methoxypsoralen and acridine) caused a dose dependent increase in lymph node weights and cell counts pointing to an inflammatory process in the lymph nodes. Analysis of cytokine gene transcription **ex vivo** and cytokine release in vitro revealed that during the induction phase of contact (photo) **allergy** CD4+ T-cells produced IL-2 and IFN-gamma as well as IL-4 and IL-10, whereas IL-6 was derived from APC. In contrast, phototoxic reactions caused only an upregulation of IL-2 and IFN-gamma. Furthermore, we demonstrate that the release of IL-4 and IL-10 by CD4+ T-cells was clearly increased, whereas IL-6 and IFN-gamma expression was reduced or not changed following a challenge with contact (photo) allergens revealing an **allergy**-indicative shift in cytokine expression. In conclusion, our results show that contact photoallergenic reactions could be differentiated from phototoxic events by analysis of LNC cytokine expression patterns.

L4 ANSWER 16 OF 17 CAPLUS COPYRIGHT 2004 ACS on STN

1996:628975 Document No. 125:273493 Murine lymph node **antigen presenting cells** are the main source of interleukin-6 in the initiation of delayed-type hypersensitivity. Ulrich, P.; Vohr, H.-W. (Inst. Toxicology, Bayer AG, Wuppertal, Germany). European Cytokine Network, 7(3), 401-407 (English) 1996. CODEN: ECYNEJ. ISSN: 1148-5493. Publisher: Libbey Eurotext.

AB Interleukin-6 (IL-6) and interferon γ (IFN-γ) production was analyzed in mice after topical exposure of the animals to Oxazolone, a well-known contact sensitizer. Since both IL-6 and IFN-γ had been shown to be involved in the initiation of delayed-type hypersensitivity (DTH) reactions, and especially in contact sensitization (CS), we focussed our anal. on the cellular source of the two cytokines in local lymph nodes draining the site of exposure. We have demonstrated that IL-6 is found exclusively in lymph node **antigen presenting cells** (LNAPC), using three different approaches: (i) in vitro restimulation of CD4-pos. cells, obtained from Oxazolone-treated mice, in the presence of I-A-pos. LNAPC, led to a strong IL-6 response, measured in culture supernatants by ELISA. Depletion of LNAPC in these suspensions prior to cultivation diminished IL-6 secretion, indicating that the LNAPC were the sole source of IL-6. (Ii) Staining of restimulated LNC for intracellular cytokines confirmed that LNAPC are the only source of IL-6 at various time-points during cultivation. (Iii) Competitive PCR anal. of cDNA, derived from freshly isolated lymph node cells (LNC) depleted either in CD8/B220- or CD8/B220/I-A-pos. cells, showed that **ex vivo** IL-6-specific mRNA was found exclusively in the LNAPC. In contrast IFN-γ is produced by CD4+ cells, although in some expts. CD8+ cells were also pos. Time-course anal. of the secretion of the two cytokines and their relation to lymphocyte blastosis in vitro showed that IL-6 peaked during the first 6 h of restimulation, whereas the number of IFN-γ producing cells reached a maximum after 24 h and were closely correlated with the increasing number of in vitro blastocytes. Our data corroborate with other authors' investigations of DTH reactions, showing that IL-6, provided by LNAPC during primary responses in vivo, may serve as a co-stimulating factor for T cells.

L4 ANSWER 17 OF 17 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN DUPLICATE 4

96210708 EMBASE Document No.: 1996210708. Novel predictive assay for contact allergens using human skin explant cultures. Pistoor F.H.M.; Rambukkana A.; Kroezen M.; Lepoittevin J.-P.; Bos J.D.; Kapsenberg M.L.; Das P.K.. Department of Pathology, Academic Medical Centre, Meibergdreef 15,1105 AZ Amsterdam, Netherlands. American Journal of Pathology 149/1 (337-343) 1996.
ISSN: 0002-9440. CODEN: AJPAA4. Pub. Country: United States. Language: English. Summary Language: English.

AB Contact allergens sensitize the immune system by the binding to and subsequent activation of Langerhans cells (LCs), the **antigen-presenting cells** of the skin. At present, new chemicals are usually tested for their contact allergenicity in animal models. To develop an animal-replacing predictive in vitro assay for the identification of potential contact allergens, we compared the effects of epicutaneous application of six known contact allergens, five known irritants and two dermatologically inactive chemicals on LCs in skin biopsy cultures from seven healthy donors. Immunohistochemical analysis of cryostat sections of all the biopsies treated with contact allergens showed 1) a large reduction in the number of LCs in epidermis as evaluated by a decrease in human leukocyte antigens (HLA)-DR-expressing cells, and CD1a-expressing cells and 2) accumulation of the remaining LCs at the epidermal-dermal junction. In contrast, the irritants, inactive chemicals, and solvents did not induce these changes. Morphometrical analysis indicated that the contact allergen-induced reduction in the number of HLA- DR+ and CD1a+ LCs per millimeter of epidermis was significant and was dependent on the concentration of the contact allergens. Flow cytometric analysis of isolated epidermal cells confirmed the immunohistochemical findings. In combination, these results suggest that the culture of

ex vivo human skin explants provides a promising model to predict potential allergenicity of newly produced chemical compounds and can therefore replace current animal models.

=> s l2 and CpG
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L6 ANSWER 1 OF 33 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN DUPLICATE 1
2004355233 EMBASE **CpG** immunostimulatory sequences enhance contact hypersensitivity responses in mice. Akiba H.; Satoh M.; Iwatsuki K.; Kaiserlian D.; Nicolas J.-F.; Kaneko F.. Dr. H. Akiba, Department of Dermatology, Fukushima Med. Univ. Sch. of Med., Hikarigaoka-1, Fukushima, 960-1295, Japan. hakiba@fmu.ac.jp. Journal of Investigative Dermatology 123/3 (488-493) 2004.
Refs: 36.
ISSN: 0022-202X. CODEN: JIDEAE. Pub. Country: United States. Language: English. Summary Language: English.
AB Bacterial DNA and synthetic cytidine-phosphate-guanosine-oligodeoxynucleotides (**CpG** ODN) potently activate dendritic cells (DC) and therefore have been proposed as adjuvants for vaccination strategies. Although **CpG** ODN are considered as safe adjuvants this study shows that **CpG** ODN are responsible for enhanced antigen-specific skin inflammatory reactions. We used the murine model of contact hypersensitivity (CHS) to 2,4-dinitrofluorobenzene (DNFB) in which hapten-specific CD8+ T cytotoxic 1 cells are effector cells. Subcutaneous injection of **CpG** ODN, 1 d before sensitization enhanced the CHS response to DNFB and resulted in increased recruitment of CD8+ T cells at the challenge sites, whereas control ODH injection did not have any effect. This effect was local and not systemic as it was only observed when DNFB was applied at the same site as the **CpG** motifs. **CpG** ODN-induced enhancement of CHS was due to increased **antigen-presenting cell** functions of DC since: (i) **CpG** ODN-injected skin revealed upregulated expression of major histocompatibility complex class II, CD80, and CD86 molecules and (ii) **CpG** ODN treatment of DNFB-derivatized DC enhanced the intensity of CHS responses after in vivo transfer. Taken together, the results show that **CpG** ODN may be responsible for immune side-effects such as worsening of T cell-mediated skin diseases.

L6 ANSWER 2 OF 33 MEDLINE on STN DUPLICATE 2
2004411482. PubMed ID: 15316529. Plasmacytoid dendritic cells activate allergen-specific TH2 memory cells: modulation by **CpG** oligodeoxynucleotides. Farkas Lorant; Kvale Espen O; Johansen Finn-Eirik; Jahnsen Frode L; Lund-Johansen Fridtjof. (Section for Immune Regulation and Allergy, LIIPAT, Institute of Pathology, Rikshospitalet University Hospital, Norway.. lorant.farkas@labmed.uio.no) . Journal of allergy and clinical immunology, (2004 Aug) 114 (2) 436-43. Journal code: 1275002.
ISSN: 0091-6749. Pub. country: United States. Language: English.
AB BACKGROUND: Plasmacytoid dendritic cells (PDCs) accumulate in the nasal mucosa of allergic rhinitis patients, but their function in upper airway **allergy** has not been determined. **CpG** oligodeoxynucleotides, potent adjuvants in immunotherapeutic strategies in animal models, are especially effective at activating PDCs. These cells are therefore potential targets for immunomodulation in humans. OBJECTIVE: In this study, PDCs were compared with CD11c+ dendritic cells (DCs), a very potent **antigen-presenting cell** type, for their capacity to induce allergen-dependent activation of TH2

memory cells. Then, we investigated whether **CpG**-activated PDCs were able to modulate the allergen-specific TH2 memory response. METHODS: DCs were isolated from patients with upper airway **allergy** and cocultured with autologous CD4+ T cells with or without grass pollen extract and **CpG**. In some experiments cells were restimulated with allergen-pulsed monocyte-derived DCs. T-cell activation was measured by their proliferative response and cytokine production. RESULTS: PDCs stimulated allergen-dependent T-cell proliferation and TH2 cytokine production as efficiently as CD11c+ DCs. **CpG**-activated PDCs inhibited allergen-dependent proliferation of TH2 memory cells and markedly increased IFN-gamma production in PDC/T-cell cocultures; the former effect depended on the **CpG**-induced IFN-alpha/beta production by the PDCs. CONCLUSION: Our results demonstrated that PDCs efficiently drive allergen-dependent TH2 memory responses, suggesting that they play an active role in the allergic reaction. However, in the presence of **CpG**, PDCs were responsible for increased production of the TH1-related cytokines IFN-alpha and IFN-gamma, indicating that mucosal PDCs may be targets for **CpG**-based immunotherapeutic strategies against airway **allergy**.

L6 ANSWER 3 OF 33 CAPLUS COPYRIGHT 2004 ACS on STN

2004:803133 Plasmacytoid dendritic cells activate allergen-specific TH2 memory cells: Modulation by **CpG** oligodeoxynucleotides. Farkas, Lorant; Kvale, Espen O.; Johansen, Finn-Eirik; Jahnsen, Frode L.; Lund-Johansen, Fridtjof (Section for Immune Regulation and Allergy, LUPAT, Institute of Pathology, Rikshospitalet University Hospital, Oslo, Norway). Journal of Allergy and Clinical Immunology, 114(2), 434-443 (English) 2004. CODEN: JACIBY. ISSN: 0091-6749. Publisher: Elsevier Inc..

AB Background: Plasmacytoid dendritic cells (PDCs) accumulate in the nasal mucosa of allergic rhinitis patients, but their function in upper airway **allergy** has not been determined **CpG** oligodeoxynucleotides, potent adjuvants in immunotherapeutic strategies in animal models, are especially effective at activating PDCs. These cells are therefore potential targets for immunomodulation in humans. Objective: In this study, PDCs were compared with CD11c+ dendritic cells (DCs), a very potent **antigen-presenting cell** type, for their capacity to induce allergen-dependent activation of TH2 memory cells. Then, we investigated whether **CpG**-activated PDCs were able to modulate the allergen-specific TH2 memory response. Methods: DCs were isolated from patients with upper airway **allergy** and cocultured with autologous CD4+ T cells with or without grass pollen extract and **CpG**. In some expts. cells were restimulated with allergen-pulsed monocyte-derived DCs. T-cell activation was measured by their proliferative response and cytokine production Results: PDCs stimulated allergen-dependent T-cell proliferation and TH2 cytokine production as efficiently as CD11c+ DCs. **CpG**-activated PDCs inhibited allergen-dependent proliferation of TH2 memory cells and markedly increased IFN-γ production in PDC/T-cell cocultures; the former effect depended on the **CpG**-induced IFN-α/β production by the PDCs. Conclusion: Our results demonstrated that PDCs efficiently drive allergen-dependent TH2 memory responses, suggesting that they play an active role in the allergic reaction. However, in the presence of **CpG**, PDCs were responsible for increased production of the TH1-related cytokines IFN-α and IFN-γ, indicating that mucosal PDCs may be targets for **CpG**-based immunotherapeutic strategies against airway **allergy**.

L6 ANSWER 4 OF 33 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

2004343666 EMBASE Developmental immunology and vaccines: Cellular immune development and future vaccine strategies. Prescott S.. Dr. S. Prescott, Sch. of Pediatrics and Child Health, University of Western Australia, Perth, WA, Australia. susanp@ichr.uwa.edu.au. Expert Review of Vaccines 3/4 (339-342) 2004.
Refs: 17.

ISSN: 1476-0584. CODEN: ERVXAX. Pub. Country: United Kingdom. Language: English. Summary Language: English.

AB This section deals with how new knowledge of the development of cellular immunity in the neonatal period informs vaccine development and reviews the immune responses of the most vulnerable group of newborns, those born prematurely, to vaccines. It describes how the development of future vaccine strategies relies on a detailed understanding of immune ontogeny and the potential consequences of intervention on developing cellular immune responses.

L6 ANSWER 5 OF 33 EMBASE
on STN

2004109460 EMBASE Mycobacteria and other environmental organisms as immunomodulators for immunoregulatory disorders. Rook G.A.W.; Adams V.; Hunt J.; Palmer R.; Martinelli R.; Brunet L.R.. G.A.W. Rook, Department of Medical Microbiology, Medical School, Royal Free and University College, 46 Cleveland Street, London, W1P 6DB, United Kingdom. g.rook@ucl.ac.uk. Springer Seminars in Immunopathology 25/3-4 (237-255) 2004. Refs: 106.
ISSN: 0344-4325. CODEN: SSIMDV. Pub. Country: Germany. Language: English. Summary Language: English.

AB In the rich, developed parts of the world there has been a steady and simultaneous increase in at least three groups of disease: (1) **allergies**, (2) inflammatory bowel diseases (IBD; e.g. Crohn's disease and ulcerative colitis) and (3) autoimmunity (e.g. type 1 diabetes and multiple sclerosis). Because the medical world is so compartmentalised it was some time before the connection between these increases was noticed and understood. There is now evidence that the simultaneous increase in these diseases of immunodysregulation is at least partly attributable to malfunction of regulatory T cells (Treg). This paper provides an overview of relevant work in each of these fields of medicine (though with emphasis on the allergic disorders), and concludes that the increasing failure of Treg is a consequence of diminished exposure to certain micro-organisms that are "old friends", because of their continuous presence throughout mammalian evolution. These organisms, which include saprophytic mycobacteria, helminths and lactobacilli, are recognised by the innate immune system as harmless, and as adjuvants for Treg induction. Polymorphisms of components of the innate immune system such as TLR2 and NOD2 appear to define subsets of the population that will develop immunoregulatory disorders when living in the modern environment. A further role of the "old friends" and of the Treg that they induce might be to maintain the levels of regulatory IL-10 secreting macrophages and **antigen-presenting cells**, which are depleted in asthma and Crohn's disease. These concepts are leading to novel therapies based on harmless organisms or their components. Phase I/II clinical trials have yielded some statistically significant results, and phase II trials are in progress.

L6 ANSWER 6 OF 33 MEDLINE on STN DUPLICATE 3

2004246630. PubMed ID: 15146108. Toll-like receptors and immune response in allergic disease. Gangloff Sophie C; Guenounou Moncef. (Department of Immunology and Microbiology, University of Reims Champagne-Ardenne, Reims, France.. Sophie.Gangloss@univ-reims.fr) . Clinical reviews in allergy & immunology, (2004 Apr) 26 (2) 115-25. Ref: 72. Journal code: 9504368.
ISSN: 1080-0549. Pub. country: United States. Language: English.

AB Allergic reactions are dominated by the preferential development of specific Th2 responses against innocuous antigens in atopic individuals. This can reflect alterations in innate immune mechanisms. Toll-like receptors (TLRs) have evolved as key molecules in innate and adaptive immunity. Their activation by structurally distinct exogenous or endogenous ligands present at the cell microenvironment plays a critical role in antimicrobial defense. The global view is that TLR activation induces **antigen-presenting cells** to produce cytokines that favor Th1-type immune responses, suggesting that it might

prevent the development of deleterious Th2 responses in **allergy**. On the basis of epidemiological studies and recent data, it has been established that TLRs play a role in the development of Th2 responses. However, more information is needed to fully understand the mechanism of TLR involvement and the implication of immune cells that express TLRs in the Th1/Th2 cytokine profiles. Several TLRs, such as TLR9, TLR7, and TLR8, can be considered as good target candidates. Some TLR ligands, such as **CpG** DNA, are effective adjuvants, strong inducers of both IL-5 and eosinophilia downregulation. They are also potential links to allergen epitopes that could provide new allergen-specific immunotherapy regimens for the treatment of allergic disorders.

L6 ANSWER 7 OF 33 CAPLUS COPYRIGHT 2004 ACS on STN
2003:991374 Document No. 140:40879 Bifunctional **CpG** or oligo-/polynucleotide and toxin or enterotoxin containing composition. Holmgren, Jan; Harandi, Ali M. (Gotovax AB, Swed.). PCT Int. Appl. WO 2003103708 A1 20031218, 46 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-SE935 20030605. PRIORITY: SE 2002-1701 20020605; US 2002-PV385588 20020605.

AB A bifunctional composition comprising an intracellularly effective immunomodulating nucleic acid component containing at least one immunostimulatory, immunoinhibitory, or immunomodulating motif and selected from a mononucleotide, a dinucleotide, an oligonucleotide or a polynucleotide with either a natural phosphodiester backbone or a modified backbone, optionally in combination with a specific antigen, in association with a protein binding to specific receptors on mammalian cell surfaces selected from the group consisting of cholera toxin (CT), the subunit B of CT (CTB), Escherichia coli heat-labile enterotoxin (LT), the subunit B of LT (LTB), and proteins or protein derivs. that react with antiserum to CT or LT, bind to GM1 ganglioside, ADP-ribosylates an acceptor protein, or give rise to accumulation of cAMP in target cells, and antibodies or other proteins which after binding to a specific cell surface component can be internalized into the cell, is described. The composition is useful for treatment of tumors, infections, graft rejections, immunosuppressive states, autoimmune diseases and **allergies**, and further with a specific antigen it is useful for immunoprophylaxis, immunotherapy or induction of tolerance, and for treatment ex vivo of an **antigen-presenting cell** for subsequent infusion into a mammal for vaccination or immunotherapy purposes.

L6 ANSWER 8 OF 33 CAPLUS COPYRIGHT 2004 ACS on STN
2003:241991 Document No. 138:270283 Oligodeoxynucleotide and its use to induce an immune response. Klinman, Dennis; Verthelyi, Daniela; Ishii, Ken; Mond, James J.; Gursel, Mayda (USA). U.S. Pat. Appl. Publ. US 2003060440 A1 20030327, 52 pp., Cont.-in-part of U.S. Ser. No. 958,713. (English). CODEN: USXXCO. APPLICATION: US 2002-68160 20020206. PRIORITY: US 1999-PV128898 19990412; US 2001-958713 20011011.

AB D type **CpG** oligodeoxynucleotides are provided herein that include a sequence represented by the following formula: 5'-X1X2X3Pu1Py2CpGPu3Py4X4X5X6(W)M(G)N-3' wherein the central **CpG** motif is unmethylated, Pu is a purine nucleotide, Py is a pyrimidine nucleotide, X and W are any nucleotide, M is any integer from 0 to 10, and N is any integer from 4 to 10. The oligodeoxynucleotides can activate immune cells, such as **antigen-presenting cells** or natural killer cell, and/or can stimulate production of cytokines. Methods of using these oligodeoxynucleotides to induce an immune response are provided. The oligodeoxynucleotides can be used in treatment or amelioration of cancer, **allergy**, autoimmune disease,

immunodeficiency, or infection. They can also be used to enhance the efficacy of vaccines.

L6 ANSWER 9 OF 33 CAPLUS COPYRIGHT 2004 ACS on STN
2003:77719 Document No. 138:135825 Therapeutic application of HIV-1 Tat protein. Ensoli, Barbara (Istituto Superiore di Sanita, Italy). Eur. Pat. Appl. EP 1279404 A1 20030129, 98 pp. DESIGNATED STATES: R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR. (English). CODEN: EPXXDW. APPLICATION: EP 2001-118114 20010726.
AB The author discloses vaccination, treatment, and diagnosis of HIV/AIDS and other infectious diseases, inflammatory and angiogenic diseases and tumors utilizing a biol. active HIV-1 Tat protein or fragments or derivs. thereof. The author discloses that Tat and Tat fragments can be characterized with one or more of the following features: as antigen, as adjuvant and targeting-delivery system to specific **antigen-presenting cells** including dendritic cells, endothelial cells and macrophages.

L6 ANSWER 10 OF 33 MEDLINE on STN DUPLICATE 4
2003502318. PubMed ID: 14568974. An immunomodulatory GpG oligonucleotide for the treatment of autoimmunity via the innate and adaptive immune systems. Ho Peggy P; Fontoura Paulo; Ruiz Pedro J; Steinman Lawrence; Garren Hideki. (Department of Neurology and Neurological Sciences, Stanford University School of Medicine, Beckman Center for Molecular Medicine, Stanford, CA 94305-5316, USA.. peggy.ho@stanford.edu) . Journal of immunology (Baltimore, Md. : 1950), (2003 Nov 1) 171 (9) 4920-6. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.
AB Bacterial DNA and immunostimulatory **CpG** oligodeoxynucleotides (ODNs) activate the innate immune system to produce proinflammatory cytokines. Shown to be potent Th1-like adjuvants, stimulatory **CpG** motifs are currently used as effective therapeutic vaccines for various animal models of infectious diseases, tumors, **allergies**, and autoimmune diseases. In this study, we show that the application of an immunomodulatory GpG ODN, with a single base switch from **CpG** to GpG, can effectively inhibit the activation of Th1 T cells associated with autoimmune disease. Moreover, this immunomodulatory GpG ODN suppresses the severity of experimental autoimmune encephalomyelitis in mice, a prototypic Th1-mediated animal disease model for multiple sclerosis.

L6 ANSWER 11 OF 33 CAPLUS COPYRIGHT 2004 ACS on STN
2003:896435 Document No. 140:57926 T cell targeted allergen derivatives for improved efficacy and safety of specific immunotherapy for allergic disease. Gardner, Leanne M.; O'Hehir, Robyn E.; Rolland, Jennifer M. (Department of Pathology and Immunology, Monash University, Melbourne, Australia). Current Medicinal Chemistry: Anti-Inflammatory & Anti-Allergy Agents, 2(4), 351-365 (English) 2003. CODEN: CMCAGM. ISSN: 1568-0142. Publisher: Bentham Science Publishers Ltd..
AB A review. Allergen-specific T cells play a pivotal role in initiating and regulating the immune response to allergens, with T cell targeted strategies showing promise for improved specific immunomodulation of the adverse immune response in allergic diseases. Atopic allergic individuals respond to allergen stimulation by dominant secretion of IL-4 and IL-5 (Th2-type cytokines) in contrast to non-atopic individuals where there is predominant IFN-γ secretion (Th1-type). Clin. effective, allergen-specific immunotherapy (SIT) is accompanied by altered allergen-specific T-cell response, notably cytokine changes of decreased IL-4 and IL-5 to IFN-γ ratio (Th2/Th1) and enhanced IL-10 secretion. Important contributing factors to these changes are likely to include the allergen concentration and form, adjuvants and **antigen presenting cell** type. Current regimens for SIT using high dose unfractionated allergen exts. injected incrementally via the s.c. route are limited by IgE-mediated adverse events, especially in asthmatic patients. Allergen derivs. with retained T cell reactivity but abrogated

IgE binding should have higher efficacy and safety. Such derivs. include peptides containing dominant T cell epitopes of allergens and chemical-modified or recombinant mutant allergen mols. Both approaches have been evaluated successfully in vivo in animal models and limited clin. trials. Th1-inducing adjuvants including bacterial components or virus-like particles, and DNA vaccines may also promote repolarization of cytokine secretion from Th2-type to Th1-type but caution is needed as excessive IFN-γ secretion may invoke exuberant pathogenic inflammation. Alternative routes for allergen administration including intranasal, oral and sublingual are also under evaluation. Full elucidation of the mechanisms underlying safer, more effective SIT should facilitate wider clin. application in the treatment of allergic diseases and the availability of reliable laboratory assays for monitoring SIT efficacy based on T cell function.

L6 ANSWER 12 OF 33 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN

2003:587355 Document No.: PREV200300587889. Advances in immunological treatment of **allergy.** Kussebi, F.; Karamloo, F.; Akdis, M.; Blaser, K.; Akdis, C. [Reprint Author]. Swiss Institute of Allergy and Asthma Research (SIAF), Obere Strasse 22, CH-7270, Davos, Switzerland. akdisac@siaf.unizh.ch. Current Medicinal Chemistry - Anti-Inflammatory & Anti-Allergy Agents, (December 2003) Vol. 2, No. 4, pp. 297-308. print. ISSN: 1568-0142 (ISSN print). Language: English.

L6 ANSWER 13 OF 33 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

2003232128 EMBASE Immunomodulation in asthma: Mechanisms and possible pitfalls. Kay A.B.. A.B. Kay, Dept. of Allergy/Clinical Immunol., Imperial College London, National Heart and Lung Institute, Guy Scadding Bldg., Dovehouse St., London SW3 6LY, United Kingdom. a.b.kay@imperial.ac.uk. Current Opinion in Pharmacology 3/3 (220-226) 2003.
Refs: 49.
ISSN: 1471-4892. CODEN: COPUBK.
Publisher Ident.: S 1471-4892(03)00038-9. Pub. Country: United Kingdom.
Language: English. Summary Language: English.

AB Atopic diseases, including atopic asthma, are characterized by T helper cell (Th)2 cytokine pathology. The increased prevalence of asthma and allergic diseases, as well as Th1-associated conditions, is linked to 'excessive' hygiene. Several new immunomodulatory strategies in asthma and **allergy**, such as peptide therapy and DNA vaccines, show promise and are under clinical evaluation. They appear to exert their effects by producing a Th2 to Th1 shift, as well as inducing regulatory cytokines such as interleukin-10 and transforming growth factor-β. There is no evidence that such approaches are associated with Th1 pathology in humans, although lung inflammation induced by Th1 cells has been observed in mice. IL-10 plays a key regulatory role in dampening both Th2- and Th1-associated diseases. Failure to stimulate regulatory responses could explain the rising trends in **allergy** and autoimmunity, and also partly explain the mode of action of allergen-injection immunotherapy and new immunomodulatory approaches.

L6 ANSWER 14 OF 33 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

2003192785 EMBASE Mucosal adjuvants and anti-infection and anti-immunopathology vaccines based on cholera toxin, cholera toxin B subunit and **CpG** DNA. Holmgren J.; Harandi A.M.; Czerkinsky C.. J. Holmgren, Department of Medical Microbiology, Goteborg Univ. Vacc. Res. Institute, Goteborg University, Guldhedsgatan 10A, SE-413 46 Goteborg, Sweden. jan.holmgren@microbio.gu.se. Expert Review of Vaccines 2/2 (205-217) 2003.
Refs: 64.
ISSN: 1476-0584. CODEN: ERVXAX. Pub. Country: United Kingdom. Language: English. Summary Language: English.

AB The mucosal immune system consists of an integrated network of lymphoid

cells that work in concert with innate host factors to promote host defence. Mucosal immunization can be used both to protect the mucosal surfaces against colonization and invasion by microbial pathogens and to provide a means for immunological treatment of selected autoimmune, allergic or infectious-immunopathological disorders through the induction of antigen-specific tolerance. The development of mucosal vaccines, whether for prevention of infectious diseases or for oral tolerance immunotherapy, requires efficient antigen delivery and adjuvant systems. Significant progress has recently been made to generate partly or wholly detoxified derivatives of cholera toxin (including the completely nontoxic cholera toxin B subunit) and the closely related Escherichia coli heat-labile enterotoxin, with retained adjuvant activity. Cholera toxin B subunit is a protective component of a widely registered oral vaccine against cholera, and has proven to be a promising vector for either giving rise to anti-infective immunity or for inducing peripheral anti-inflammatory tolerance to chemically or genetically linked foreign antigens administered mucosally. Promising advances have also recently been made In the design of efficient mucosal adjuvants based on bacterial DNA that contains **CpG**-motifs and various imidazoquinoline compounds binding to different Toll-like receptors on mucosal **antigen-presenting cells.**

L6 ANSWER 15 OF 33 SCISEARCH COPYRIGHT (c) 2004 The Thomson Corporation. on STN

2003:308072 The Genuine Article (R) Number: 662NA. Recent advances in the development of immunostimulatory oligonucleotides. Uhlmann E (Reprint); Vollmer J. Coley Pharmaceut GmbH, Elisabeth Selbert Str 9, D-40764 Langenfeld, Germany (Reprint); Coley Pharmaceut GmbH, D-40764 Langenfeld, Germany. CURRENT OPINION IN DRUG DISCOVERY & DEVELOPMENT (MAR 2003) Vol. 6, No. 2, pp. 204-217. Publisher: CURRENT DRUGS LTD. MIDDLESEX HOUSE, 34-42 CLEVELAND ST, LONDON W1P 6LB, ENGLAND. ISSN: 1367-6733. Pub. country: Germany. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Some immune cells recognize distinct molecular structures present in pathogens through specific pattern recognition receptors that are able to distinguish prokaryotic DNA from vertebrate DNA. The detection of invading microbial DNA is based on the recognition of unmethylated deoxycytidyl-deoxyguanosin dinucleotide (**CpG**) motifs. Synthetic oligonucleotides (ODNs) containing these **CpG** motifs are able to activate both innate and acquired immune responses through a signaling pathway involving Toll-like receptor 9 (TLR9). Depending an the sequence, length, as well as number and positions of **CpG** motifs in an ODN, distinct immunostimulatory profiles can be observed. These immunostimulatory profiles can be further modified and fine-tuned by appropriate chemical modifications, leading to preclinical and clinical development of **CpG** ODNs in cancer, **allergy**, asthma and infectious diseases.

L6 ANSWER 16 OF 33 SCISEARCH COPYRIGHT (c) 2004 The Thomson Corporation. on STN

2003:599455 The Genuine Article (R) Number: 699WY. DNA immunostimulation: A novel therapeutic approach for allergic diseases. Petering H (Reprint); Werfel T; Kapp A. Hannover Med Sch, Klin & Poliklin Dermatol & Venerol, Ricklinger Str 5, D-30449 Hannover, Germany (Reprint); Hannover Med Sch, Klin & Poliklin Dermatol & Venerol, D-30449 Hannover, Germany. ALLERGOLOGI E (MAY 2003) Vol. 26, No. 5, pp. 202-211. Publisher: DUSTRI-VERLAG DR KARL FEISTLE. BAJUWARENRING 4, D-82041 OBERHACHING, GERMANY. ISSN: 0344-5062. Pub. country: Germany. Language: German.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Some studies have linked the rise of atopy with an increase in living standards' immunization programs and antibiotic therapy. This has led to the theory that, while the normal response to childhood infections is the deviation of the immune system to a TH1-type cytokine response, the absence of these infections in industrialized countries has resulted in the predominance of an atopy-associated TH2-type response. Therefore,

bacterial infections in childhood seem to have protective effects against a predominant TH2-type cytokine pattern, and immunostimulatory DNA sequences (**CpG** motifs) in bacterial DNA are gaining recognition as potential immunomodulators for switching on protective TH1-mediated immunity and preventing or potentially inhibiting TH2-dependent allergic responses. This review article starts with a description of the TH1/TH2 paradigm as a conceptional framework for T helper cell differentiation in atopic disorders followed by an illustration of the structure of immunostimulatory DNA sequences and their effector functions on different cell types. In addition, this article provides insight into the potential therapeutic application of **CpG**-DNA in allergic diseases.

L6 ANSWER 17 OF 33 SCISEARCH COPYRIGHT (c) 2004 The Thomson Corporation. on STN

2003:503250 The Genuine Article (R) Number: 688KP. Toll-like receptors and T-helper-1/T-helper-2 responses. Dabbagh K (Reprint); Lewis D B. Roche Palo Alto, Resp Dis, MS S3-1, 3401 Hillview Ave, Palo Alto, CA 94304 USA (Reprint); Roche Palo Alto, Resp Dis, Palo Alto, CA 94304 USA; Stanford Univ, Sch Med, Dept Pediat, Div Immunol Transplantat Biol, Stanford, CA 94305 USA. CURRENT OPINION IN INFECTIOUS DISEASES (JUN 2003) Vol. 16, No. 3, pp. 199-204. Publisher: LIPPINCOTT WILLIAMS & WILKINS. 530 WALNUT ST, PHILADELPHIA, PA 19106-3621 USA. ISSN: 0951-7375. Pub. country: USA. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Purpose of review Toll-like receptors (TLRs) are a family of pattern recognition receptors that are activated by specific components of microbes and certain host molecules. They constitute the first line of defense against many pathogens and play a crucial role in the function of the innate immune system. Recently, TLRs were observed to influence the development of adaptive immune responses, presumably by activating **antigen-presenting cells.** This has important implications for our understanding of how the host tailors its immune response as a function of specific pathogen recognition. The present review discusses the recent studies that demonstrate the role of TLRs in the regulation of adaptive T-helper-1 (Th1) and Th2 responses, and the mechanisms by which the effects are carried out.

Recent findings Most studies have focused on the role of TLRs and components of their signaling pathways in the control of Th1-type immune responses, and on the implications for their use as antimicrobial agents, such as adjuvants in vaccines, or to treat or prevent the Th2-type dominated immune responses seen in **allergies.** TLR-deficient mice have been described and used to come to these conclusions. Although controversial, there is also evidence that TLRs may be important for Th2-type responses, possibly by augmenting the overall maturity of dendritic cells.

Summary A greater understanding of the processes by which TLRs regulate adaptive immunity may yield not only improved ways to treat infectious diseases but also new approaches to the treatment and prevention of allergic and certain autoimmune disorders.

L6 ANSWER 18 OF 33 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

2003216025 EMBASE Enhancing immunogenicity by **CpG** DNA. Jiang W.; Pisetsky D.S.. D.S. Pisetsky, Durham VA Medical Center, 508 Fulton Street, Durham, NC 27705, United States. piset001@mc.duke.edu. Current Opinion in Molecular Therapeutics 5/2 (180-185) 2003.

Refs: 75.

ISSN: 1464-8431. CODEN: CUOTFO. Pub. Country: United Kingdom. Language: English. Summary Language: English.

AB Bacterial DNA and oligonucleotides containing unmethylated **CpG** dinucleotides (**CpG** DNA) can stimulate immune responses and have potential for use as novel agents to enhance immunogenicity. **CpG** DNA can interact with toll-like receptor 9 and cause activation through a myeloid differentiation primary response gene (MyD88)-dependent signaling pathway. Due to its pattern of immune cell activation, **CpG** DNA

can induce a cytokine milieu to promote T-helper cell responses and serve as an adjuvant. Furthermore, **CpG** DNA can provide protection against pathogens in animal models and has therapeutic applications in clinical settings such as in cancer and **allergy.**

L6 ANSWER 19 OF 33 SCISEARCH COPYRIGHT (c) 2004 The Thomson Corporation. on STN

2003:74638 The Genuine Article (R) Number: 633DQ. **CpG** -oligonucleotides for cancer immunotherapy: Review of the literature and potential applications in malignant glioma. Carpentier A F (Reprint); Auf G; Delattre J Y. Hop La Pitie Salpetriere, Federat Neurol Mazarin, 47 Blvd Hop, F-75013 Paris, France (Reprint); Hop La Pitie Salpetriere, Federat Neurol Mazarin, F-75013 Paris, France; Univ Paris 06, INSERM, U495, Hop Broussais, UPRES 264, F-75014 Paris, France. FRONTIERS IN BIOSCIENCE (JAN 2003) Vol. 8, pp. E115-E127. Publisher: FRONTIERS IN BIOSCIENCE INC. C/O NORTH SHORE UNIV HOSPITAL, BIOMEDICAL RESEARCH CENTER, 350 COMMUNITY DR, MANHASSET, NY 11030 USA. ISSN: 1093-9946. Pub. country: France. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Bacterial DNA and synthetic oligodeoxynucleotides containing **CpG** motifs (**CpG**-ODNs) are strong activators of both innate and specific immunity, driving the immune response towards the Th1 phenotype. **CpG**-ODNs have been successfully used in several experimental models of **allergies** or infections and are now entering clinical trials for these diseases. In this review, we will focus on their potential applications in cancers. **CpG**-ODN can be used alone to activate locally the innate immunity and trigger a tumor-specific immune response, overcoming the need for identification of a relevant tumoral antigen. Other promising approaches combined **CpG**-ODN with tumor antigens, monoclonal antibodies or dendritic cells. Preclinical models have shown impressive results and several clinical trials are on-going worldwide. So far, the toxicity observed in humans appeared limited, and objective responses have been observed in a few patients. In malignant gliomas, intra-tumoral injections of **CpG**-ODN represent a practical approach. Indeed, human gliomas display a locally invasive pattern of growth and rarely metastasize, making local treatment clinically relevant.

L6 ANSWER 20 OF 33 SCISEARCH COPYRIGHT (c) 2004 The Thomson Corporation. on STN

2002:330865 The Genuine Article (R) Number: 541XV. **CpG** motifs in bacterial DNA and their immune effects. Krieg A M (Reprint). Dept Vet Affairs Med Ctr, Iowa City, IA 52246 USA (Reprint); Univ Iowa, Coll Med, Dept Internal Med, Iowa City, IA 52242 USA; Coley Pharmaceut Grp, Wellesley, MA 02481 USA. ANNUAL REVIEW OF IMMUNOLOGY (MAR 2002) Vol. 20, pp. 709-760. Publisher: ANNUAL REVIEWS. 4139 EL CAMINO WAY, PO BOX 10139, PALO ALTO, CA 94303-0139 USA. ISSN: 0732-0582. Pub. country: USA. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Unmethylated **CpG** motifs are prevalent in bacterial but not vertebrate genomic DNAs. Oligodeoxynucleotides (ODN) containing **CpG** motifs activate host defense mechanisms leading to innate and acquired immune responses. The recognition of **CpG** motifs requires Toll-like receptor (TLR) 9, which triggers alterations in cellular redox balance and the induction of cell signaling pathways including the mitogen activated protein kinases (MAPKs) and NFkappaB. Cells that express TLR-9, which include plasmacytoid dendritic cells (PDCs) and B cells, produce Th1-like proinflammatory cytokines, interferons, and chemokines. Certain **CpG** motifs (**CpG** -A) are especially potent at activating NK cells and inducing IFN-alpha production by PDCs, while other motifs (**CpG**-B) are especially potent B cell activators. **CpG**-induced activation of innate immunity protects against lethal challenge with a wide variety of pathogens, and has therapeutic activity in murine models of cancer and **allergy. CpG** ODN also enhance the development of

acquired immune responses for prophylactic and therapeutic vaccination.

L6 ANSWER 21 OF 33 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

2002441539 EMBASE Immunostimulatory sequence oligodeoxynucleotide-based vaccination and immunomodulation: Two unique but complementary strategies for the treatment of allergic diseases. Horner A.A.; Raz E.. Dr. A.A. Horner, University of California San Diego, 9500 Gilman Dr, San Diego, CA 92093-0663, United States. Journal of Allergy and Clinical Immunology 110/5 (706-712) 2002.
Refs: 54.
ISSN: 0091-6749. CODEN: JACIBY. Pub. Country: United States. Language: English. Summary Language: English.

AB Despite a number of effective pharmaceutical options for the prevention and treatment of the pathophysiologic responses that occur in sensitized patients on allergen exposure, the termination of allergic hypersensitivities remains an elusive therapeutic goal. Traditional immunotherapy with allergen extracts is the only currently used intervention that has been shown to induce allergen tolerance, but it has a limited scope of efficacy. However, recent studies suggest that immunostimulatory sequence oligodeoxynucleotide (ISS-ODN)-based interventions might offer an alternative and potentially more effective means for extinguishing T(H)2-biased hypersensitivities. Three basic ISS-ODN-based immunotherapeutic strategies have been studied to date. Immunization with allergen mixed with ISS-ODN, immunization with allergen-ISS-ODN conjugates, and immunomodulation with ISS-ODN alone all have proved efficacy in the attenuation of the allergic phenotype in mice. Preliminary results with allergen-ISS-ODN conjugate vaccines in allergic patients have also been encouraging. This article will provide our perspective on the application of ISS-ODN-based vaccination and immunomodulation to the treatment of atopic diseases and the immunologic basis for their antiallergic activities.

L6 ANSWER 22 OF 33 SCISEARCH COPYRIGHT (c) 2004 The Thomson Corporation. on STN

2002:731537 The Genuine Article (R) Number: 586XG. Identification of CD11c+ myeloid dentritic cells in adenoids and in nasal mucosa of patients with and without **allergies.** Tuma E; Rothenfusser S; Hartmann G; Wollenberg B (Reprint). Univ Munich, Klinikum Grosshadern, Klin & Poliklin Hals Nasen & Ohrenkranke, Marchioninistr 15, D-81377 Munich, Germany (Reprint); Univ Munich, Klinikum Grosshadern, Klin & Poliklin Hals Nasen & Ohrenkranke, D-81377 Munich, Germany; Univ Munich, Klin Pharmakol Abt, Med Klin, D-81377 Munich, Germany. LARYNGO-RHINO-OTOLOGIE (AUG 2002) Vol. 81, No. 8, pp. 580-585. Publisher: GEORG THIEME VERLAG KG. RUDIGERSTR 14, D-70469 STUTTGART, GERMANY. ISSN: 1615-0007. Pub. country: Germany. Language: German.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Background: Dendritic cells form a link between innate and acquired immunity. They are capable to detect pathogens based on the recognition of pathogen-associated microbial molecules and trigger the appropriate type of immune responses. In humans, three major subsets of dendritic cells can be distinguished, Langerhans cells of the skin, myeloid DC (MDC) and plasmacytoid DC (PDC). It was reported that PDC infiltrate nasal mucosa in allergen-induced rhinits. Information about the role of MDC in nasal mucosa and the corresponding mucosa-associated lymphoid tissue, the nasopharyngeal adenoids, is limited.

Patients and Methods: Here we examined the presence of MDC in adenoids and in nasal mucosa of healthy individuals (n = 9) and in patients with allergic rhinits. MDC were detected by flow cytometry by positive staining for MHC II and CD11c and the lack of lineage markers. Dead cells were excluded from analysis.

Results: In adenoids, 0.4% of all cells were MDC. Considerable numbers of MDC could also be detected in nasal mucosa. No difference was found between healthy individuals and patients with **allergies** (0.3% vs. 0.45% MDC; p = 0.12). Interestingly, MDC were absent in patients who

received treatment with glucocorticoids, while very high numbers of MDC were found in patients who recently had upper respiratory tract infections.

Conclusion: Our results demonstrate for the first time the presence of MDC in nasal mucosa. MDC numbers were similar in healthy individuals and in patients with **allergy.** This study forms the basis for examining the role of MDC in the pathogenesis of allergic rhinitis, and for the modulation of MDC functional activity with microbial molecules such as **CpG** oligonucleotides.

L6 ANSWER 23 OF 33 CAPLUS COPYRIGHT 2004 ACS on STN

2002:838709 Document No. 138:135278 Immunostimulatory DNA for allergic asthma. Ikeda, Reid K.; Takabayashi, Kenji; Broide, David (Department of Medicine, University of California at San Diego, La Jolla, CA, USA). Microbial DNA and Host Immunity, 289-299. Editor(s): Raz, Eyal. Humana Press Inc.: Totowa, N. J. ISBN: 1-58829-022-0 (English) 2002. CODEN: 69DFSH.

AB A review discusses mechanisms of action and potential efficacy of DNA-based approach, with emphasis on the immunostimulatory sequence (ISS)-protein allergen conjugate therapy, in the treatment of asthma. Exon-coding DNA vaccines are designed to inhibit T helper 2 (Th2) immune response to specific DNA encoded allergens. ISS therapy redirects the host immune response from Th2 to a Th1 response. ISS-allergen protein conjugate therapy improves the efficacy of unconjuagated ISS therapy by targeting ISS and the protein allergen to the same **antigen-presenting cell.**

L6 ANSWER 24 OF 33 SCISEARCH COPYRIGHT (c) 2004 The Thomson Corporation. on STN

2001:978864 The Genuine Article (R) Number: 498RG. Multistep navigation of Langerhans/dendritic cells in and out of the skin. Jakob T (Reprint); Ring J; Udey M C. Tech Univ Munich, Dept Dermatol & Allergy Biederstein, Div Environm Dermatol & Allergy GSF TUM, Biedersteiner Str 29, D-80802 Munich, Germany (Reprint); Tech Univ Munich, Dept Dermatol & Allergy Biederstein, Div Environm Dermatol & Allergy GSF TUM, D-80802 Munich, Germany; GSF, Natl Res Ctr Environm & Hlth, Div Environm Dermatol & Allergy GSF TUM, Neuherberg, Germany; NCI, Dermatol Branch, NIH, Bethesda, MD 20892 USA. JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY (NOV 2001) Vol. 108, No. 5, pp. 688-696. Publisher: MOSBY, INC. 11830 WESTLINE INDUSTRIAL DR, ST LOUIS, MO 63146-3318 USA. ISSN: 0091-6749. Pub. country: Germany; USA. Language: English.

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Langerhans cells (LCs) are specialized **antigen-presenting cells** that reside in the epidermis as sentinels of the immune system. LCs constantly monitor the epidermal microenvironment by taking up antigen and processing it into fragments that can be recognized by cells of the adaptive immune response. Because of their unique migratory ability, LCs can transport antigen from the epidermis to regional lymph nodes, where they can initiate systemic immune responses. The mechanisms of LC trafficking thus seem to be of particular relevance for the induction and maintenance of cutaneous immunity. LCs or their putative precursors express surface molecules that allow them to home to skin and localize in the epidermis for prolonged periods of time. Tissue injury, microbial infection, and other perturbants of epidermal homeostasis (eg, contact allergens) provide danger signals, leading to a local production of proinflammatory cytokines that induce LC mobilization to the lymphoid tissue. At the same time, signals are generated that recruit LC precursors into the skin to maintain the epidermal LC population. Distinct pairs of chemokines and their receptors control the migration from blood to epidermis and from there to the regional lymphatics. In addition, trafficking is controlled at the level of cell adhesion, where LCs downregulate some adhesion molecules to exit the epidermis and upregulate others to migrate across the extracellular matrix and home to T-cell areas of regional lymphoid tissue. The improved understanding of mechanisms that regulate LC trafficking might offer new

opportunities for therapeutic interventions to suppress, stimulate, or deviate cutaneous immune responses.

L6 ANSWER 25 OF 33 SCISEARCH COPYRIGHT (c) 2004 The Thomson Corporation. on STN

2001:442145 The Genuine Article (R) Number: 437BW. **Allergy** Review Series VII: Intracellular signaling and regulation of allergic reactions - **CPG** oligonucleotide modulation of allergic inflammation. Wild J S; Sur S (Reprint). Univ Texas, Med Branch, Dept Internal Med, Div Allergy & Immunol, 8-104 MRB, 301 Univ Blvd, Galveston, TX 77555 USA (Reprint); Univ Texas, Med Branch, Dept Internal Med, Div Allergy & Immunol, Galveston, TX 77555 USA. ALLERGY (MAY 2001) Vol. 56, No. 5, pp. 365-376. Publisher: MUNKSGAARD INT PUBL LTD. 35 NORRE SOGADE, PO BOX 2148, DK-1016 COPENHAGEN, DENMARK. ISSN: 0105-4538. Pub. country: USA. Language: English .

L6 ANSWER 26 OF 33 CAPLUS COPYRIGHT 2004 ACS on STN

2000:741936 Document No. 133:308997 Methods for skewing the balance between Th1 and Th2 immune responses. Bottomly, H. Kim; Caplan, Michael J.; Sosin, Howard B. (Panacea Pharmaceuticals, LLC, USA). PCT Int. Appl. WO 2000061157 A1 20001019, 76 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US9270 20000407. PRIORITY: US 1999-290029 19990409.

AB The present invention provides compns. and methods for regulating immune system reactions by biasing T cell responses away from Th1 or Th2 responses in a pre-determined manner. Control is effected at the stage of antigen/APC encounter and/or at the stage of APC/T cell encounter. In preferred embodiments, a Th1 or Th2 response is inhibited through induction of the alternative response. The inventive methods and reagents are particularly useful for the management of autoimmune disorders, **allergy**, and asthma.

L6 ANSWER 27 OF 33 MEDLINE on STN DUPLICATE 5

2003398000. PubMed ID: 12937643. Immunotherapeutic applications of **CpG**-containing oligodeoxynucleotides. Klinman D M; Ishii K J; Gursel M; Gursel I; Takeshita S; Takeshita F. (Section of Retroviral Research, Center for Biologics Evaluation and Research, Food and Drug Administration, Bethesda, Maryland 20892, USA.) Drug news & perspectives, (2000 Jun) 13 (5) 289-96. Journal code: 8809164. ISSN: 0214-0934. Pub. country: Spain. Language: English.

AB Bacterial DNA and synthetic oligodeoxynucleotides (ODN) expressing unmethylated **CpG** motifs stimulate the mammalian immune system to mount a rapid innate immune response. This response is characterized by the production of polyreactive IgM, immunomodulatory cytokines and chemokines. **CpG** ODN directly stimulate lymphocytes, natural killer cells and professional **antigen-presenting cells** (such as macrophages and dendritic cells). Owing to the strength and nature of this stimulation, **CpG** ODN are being harnessed for a variety of therapeutic uses. They are being tested for their ability to act as immune adjuvants, boosting the immune response elicited by conventional and DNA vaccines. As a result of their ability to activate a strong interferon gamma-dominated Th1 response while blocking the development of Th2-dependent **allergies**, **CpG** ODN are being examined for their antiallergic properties. Finally, **CpG** ODN are being used as "immunoprotective agents", since the innate immune response they elicit can protect the host from a variety of pathogenic bacteria, viruses and parasites.

L6 ANSWER 28 OF 33 MEDLINE on STN

2000171150. PubMed ID: 10705218. **CpG** DNA as a Th1 trigger. Heeg K; Zimmermann S. (Institute of Medical Microbiology and Hygiene, Philipps University of Marburg, Marburg, Germany.. heeg@post.med.uni-marburg.de) . International archives of allergy and immunology, (2000 Feb) 121 (2) 87-97. Ref: 128. Journal code: 9211652. ISSN: 1018-2438. Pub. country: Switzerland. Language: English.

AB Over the last few years, it has been recognized that along with structural components and products of bacteria, bacterial DNA is also capable of signaling infectious danger to cells of the innate immune system. Particular DNA sequences (**CpG** motifs), which are abundant in prokaryotic (bacterial) but not in mammalian DNA, cause the activation and stimulation of immune cells. Research has been catalyzed by the finding that certain synthetic oligodeoxynucleotides mimic the action of bacterial DNA. Immunostimulation induced by bacterial DNA or synthetic oligonucleotides not only contributes to our knowledge of the pathogen-host interrelationship during infection, but can also be used therapeutically to condition or modify ongoing immune responses of the adaptive immune system. Accordingly, **CpG** motifs have been used as vaccine adjuvants as well as instructing agents to selectively induce Th1-dominated immune responses. Hence, **CpG** motifs might be used in the future as adjuvants and/or immunomodulatory agents to treat or prevent undesired Th2-dominated immune responses, such as **allergy** .

L6 ANSWER 29 OF 33 EMBASE on STN

2000063682 EMBASE The role of **CpG** motifs in innate immunity. Krieg A.M.. A.M. Krieg, Dept. Veterans Affairs Medical Ctr., Department of Internal Medicine, University Iowa College of Medicine, Iowa City, IA 52242, United States. arthur-krieg@uiowa.edu. Current Opinion in Immunology 12/1 (35-43) 2000.
Refs: 98.
ISSN: 0952-7915. CODEN: COPIEL. Pub. Country: United Kingdom. Language: English. Summary Language: English.

AB Pattern recognition receptors of the innate immune system are able to distinguish certain prokaryotic DNAs from vertebrate DNAs by detecting unmethylated **CpG** dinucleotides in particular base contexts (' **CpG** motifs'). Recent studies have begun to define the molecular mechanisms of actions of **CpG** motifs and have demonstrated their stimulatory effects on leukocytes from humans and vertebrates other than mice. Oligodeoxynucleotides containing **CpG** motifs are highly effective Th1-like vaccine adjuvants through multiple routes of immunization and show promise as immunotherapeutic agents for cancer and allergic diseases.

L6 ANSWER 30 OF 33 MEDLINE on STN DUPLICATE 6

2000153302. PubMed ID: 10686503. Genetic and environmental factors contributing to the onset of allergic disorders. Parronchi P; Brugnolo F; Sampognaro S; Maggi E. (Department of Internal Medicine, Immunoallergology and Respiratory Disease Unit, University of Florence, Italy.) International archives of allergy and immunology, (2000 Jan) 121 (1) 2-9. Ref: 88. Journal code: 9211652. ISSN: 1018-2438. Pub. country: Switzerland. Language: English.

AB Evidence has been accumulated to suggest that allergen-reactive Th2 cells play a triggering role in the activation and/or recruitment of IgE antibody-producing B cells, mast cells and eosinophils, the cellular triad involved in allergic inflammation. Recently, chemokines and chemokine receptors involved in such Th2-type response have been also defined. Th2 cells represent the polarized arm of the effector-specific responses that contribute to the protection against gastrointestinal nematodes and act as regulatory cells for chronic and/or excessive Th1-mediated responses. Th2 cells are generated from precursor naive Th cells when they encounter the specific antigen in an IL-4-containing microenvironment. The question of how these Th2 cells are selected in atopic patients is also unclear. Both

the nature of the T cell receptor signalling provided by the allergen peptide ligand and a disregulation of IL-4 production likely concur to determine the Th2 profile of allergen-specific Th cells, but the genetic unbalanced IL-4 production is certainly overwhelming. Some gene products selectively expressed in Th2 cells or selectively controlling the expression of IL-4 have recently been described. These findings allow to suggest that the upregulation of genes controlling IL-4 expression and/or abnormalities of regulatory mechanisms of Th2 development and/or function may be responsible for Th2 responses against allergens in atopic people. The increasing prevalence of **allergy** in developed countries suggests that environmental factors acting either before or after birth also contribute to regulate the development of Th2 cells and/or their function. The reduction of infectious diseases in early life due to increasing vaccinations, antimicrobial treatments as well as changed lifestyle are certainly important in influencing the individual outcome in the Th response to ubiquitous allergens. Moreover, the recent evidence that bacterial DNA or oligodeoxynucleotides containing unmethylated ' **CpG** motifs' promote the development of Th1 cells via the production of immunomodulatory cytokines (namely IL-12, IL-18 and IFNs) by professional **antigen-presenting cells** confirms previous epidemiological data. The new insight into the pathophysiology of T cell responses in atopic diseases provides exciting opportunities for the development of novel immunotherapeutic strategies. Copyright 2000 S. Karger AG, Basel

L6 ANSWER 31 OF 33 SCISEARCH COPYRIGHT (c) 2004 The Thomson Corporation. on STN

1999:616328 The Genuine Article (R) Number: 223HL. **CpG** DNA: A potent signal for growth, activation, and maturation of human dendritic cells. Hartmann G; Weiner G J; Krieg A M (Reprint). UNIV IOWA, DEPT INTERNAL MED, 540 EMRB, IOWA CITY, IA 52242 (Reprint); UNIV IOWA, DEPT INTERNAL MED, IOWA CITY, IA 52242; UNIV IOWA, CTR CANC, IOWA CITY, IA 52242; VET AFFAIRS MED CTR, IOWA CITY, IA 52246; CPG IMMUNOPHARMACEUT GMBH, D-40724 HILDEN, GERMANY; CPG IMMUNOPHARMACEUT INC, WELLESLEY, MA 02481. PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA (3 AUG 1999) Vol. 96, No. 16, pp. 9305-9310. Publisher: NATL ACAD SCIENCES. 2101 CONSTITUTION AVE NW, WASHINGTON, DC 20418. ISSN: 0027-8424. Pub. country: USA; GERMANY. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB DNA molecules containing unmethylated **CpG**-dinucleotides in particular base contexts (''**CpG** motifs'') are excellent adjuvants in rodents, but their effects on human cells have been less clear. Dendritic cells (DCs) form the link between the innate and the acquired immune system and may influence the balance between T helper 1 (Th1) and Th2 immune responses. We evaluated the effects of **CpG** oligodeoxynucleotides alone or in combination with granulocyte-macrophage colony-stimulating factor (GMCSF) on different classes of purified human DCs, For primary dendritic precursor cells isolated from human blood, **CpG** oligonucleotides alone were superior to GMCSF in promoting survival and maturation (CD83 expression) as well as expression of class Ii MHC and the costimulatory molecules CD40, CD54, and CD86 of DCs, Both CD4-positive and CD4-negative peripheral blood dendritic precursor cells responded to **CpG** DNA which synergized with GMCSF but these DCs showed little response to lipopolysaccharide (LPS). In contrast, monocyte-derived DCs did not respond to **CpG**, but they were highly sensitive to LPS, suggesting an inverse correlation between **CpG** and LPS sensitivity in different subsets of DCs. Compared with GMCSF, **CpG**-treated peripheral blood DCs showed enhanced functional activity in the mixed lymphocyte reaction and induced T cells to secrete increased levers of Th1 cytokines, These findings demonstrate the ability of specific **CpG** motifs to strongly activate certain subsets of human DCs to promote Th1-like immune responses, and support the use of **CpG** DNA-based trials for immunotherapy against cancer, **allergy**, and infectious diseases.

L6 ANSWER 32 OF 33 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

2000008596 EMBASE Macrophage activation by immunostimulatory DNA. Stacey K.J.; Sester D.P.; Sweet M.J.; Hume D.A.. K.J. Stacey, Ctr. for Molec. and Cellular Biology, Dept. of Biochemistry and Microbiol., University of Queensland, Brisbane, QLD 4072, Australia. K.Stacey@cmcb.uq.edu.au. Current Topics in Microbiology and Immunology 247/- (41-58) 1999. Refs: 80.
ISSN: 0070-217X. CODEN: CTMIA3. Pub. Country: Germany. Language: English. Summary Language: English.

AB Macrophage/dendritic cells and B cells remain the only cell types where direct responses to **CpG** DNA are well established. The role of macrophages in vivo in DNA clearance and the potent cytokine induction in macrophages and dendritic cells places them in the central role in the in vivo response to foreign DNA. Although responses to DNA are unlikely to evolve and be retained if they are not significant in the immune response to infection, the relative contributions of DNA and other stimulators of the innate immune recognition of foreign organisms is difficult to assess. Although **CpG** DNA and LPS have similar actions, significant differences are emerging that make the use of DNA as a therapeutic immunostimulatory molecule feasible. The macrophage response to DNA generates cytokines favouring the development of Th1-type immunity, and active oligonucleotides now show promise as Th1-promoting adjuvants and as **allergy** treatments.

L6 ANSWER 33 OF 33 SCISEARCH COPYRIGHT (c) 2004 The Thomson Corporation. on STN

1998:724532 The Genuine Article (R) Number: 119YB. Bacterial DNA as an evolutionary conserved ligand signalling danger of infection to immune cells. Heeg K (Reprint); Sparwasser T; Lipford G B; Hacker H; Zimmermann S; Wagner H. TECH UNIV MUNICH, INST MED MICROBIOL IMMUNOL & HYG, TROGERSTR 39, D-81675 MUNICH, GERMANY (Reprint). EUROPEAN JOURNAL OF CLINICAL MICROBIOLOGY & INFECTIOUS DISEASES (JUL 1998) Vol. 17, No. 7, pp. 464-469. Publisher: MMW MEDIZIN VERLAG GMBH. MUNCHEN, SUBSCRIPTION DEPT, D-81664 MUNICH, GERMANY. ISSN: 0934-9723. Pub. country: GERMANY. Language: English .

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB During infection, the innate limb of the immune system senses danger (pathogens) via constitutively expressed pattern-recognition receptors, and responds with activation and secretion of pro-inflammatory cytokines. Cell-wall components of gram-positive and gram-negative bacteria, such as peptidoglycan, endotoxin or lipoteichoic acid, activate via CD14, a prototypic pattern-recognition receptor for carbohydrates. This review article focuses on an alternative recognition system of the innate immune system for the recognition of bacterial DNA. Bacterial DNA differs from eukaryotic DNA in its frequency of the dinucleotides CG and its lack of methylation. These structural differences appear to be sensed by cells of the innate immune system such as **antigen-presenting cells.** As a consequence bacterial DNA serves as an alternate ligand to signal danger of infection. Bacterial DNA and (synthetic) oligonucleotides (ODN) derived thereof are as efficient as endotoxin in activating macrophages and dendritic cells and ill triggering release of pro-inflammatory cytokines. In mice sensitized with D-galactosamine (D-GalN), high doses of bacterial DNA from either gram-positive or gram-negative pathogens induce a lethal cytokine syndrome (lethal shock). Therefore, bacterial DNA may represent a hitherto unrecognized pathophysiological entity in host-parasite interactions. Moreover, recent evidence suggests that bacterial DNA or immunostimulating ODN triggers the immunostimulation of **antigen-presenting cells** , and can be utilized as adjuvant to enhance immune responses of the adaptive immune system towards poorly immunogenic antigens, In fact, foreign DNA might be useful as immunotherapeutically active adjuvant to direct adaptive immune responses towards Th1-dominated immune reactions. If these findings are operative in humans, immunostimulating ODN might be used to influence Th2-dominated diseases such as **allergy.**

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     FILE 'MEDLINE, EMBASE, BIOSIS, SCISEARCH, CAPLUS' ENTERED AT 13:16:16 ON
     14 DEC 2004
L1         59137 S ANTIGEN PRESENTING CELL
L2          1515 S L1 AND ALLERGY
L3            30 S L2 AND EX VIVO
L4            17 DUP REMOVE L3 (13 DUPLICATES REMOVED)
L5            48 S L2 AND CPG
L6            33 DUP REMOVE L5 (15 DUPLICATES REMOVED)

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L7             2 L2 AND HEAT KILLED LISTERIA

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PROCESSING COMPLETED FOR L7
L8             2 DUP REMOVE L7 (0 DUPLICATES REMOVED)

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L8   ANSWER 1 OF 2  CAPLUS  COPYRIGHT 2004 ACS on STN
2003:534047   Document No. 139:132416  Induction of interleukin-12 production
     in mouse macrophages by berberine, a benzodioxoloquinolizine alkaloid,
     deviates CD4+ T cells from a Th2 to a Th1 response.  Kim, Tae S.; Kang,
     Bok Y.; Cho, Daeho; Kim, Seung H. (College of Pharmacy and Research
     Institute of Drug Development, Chonnam National University, Kwangju, S.
     Korea).  Immunology, 109(3), 407-414 (English) 2003.  CODEN: IMMUAM.
     ISSN: 0019-2805.  Publisher: Blackwell Publishing Ltd..
AB   In this study we investigated whether berberine-mediated induction of
     interleukin-12 (IL-12) production in antigen-presenting
     cells could regulate a cytokine profile of antigen-primed CD4+ T
     helper (Th) cells.  Pretreatment with berberine induced IL-12 production in
     both macrophages and dendritic cells, and significantly increased the
     levels of IL-12 production in lipopolysaccharide-stimulated macrophages and in
     CD40 ligand-stimulated dendritic cells.  Importantly, berberine
     pretreatment of macrophages increased their ability to induce
     interferon-γ (IFN-γ) and reduced their ability to induce IL-4
     in antigen-primed CD4+ T cells.  Berberine did not influence the
     macrophage cell surface expression of the class II major
     histocompatibility complex mol., the co-stimulatory mols. CD80 and CD86,
     and intracellular adhesion mol.-1.  Addition of neutralizing anti-IL-12p40
     monoclonal antibody to cultures of berberine-pretreated macrophages and
     CD4+ T cells restored IL-4 production in antigen-primed CD4+ T cells.  The in
     vivo administration of berberine resulted in the enhanced induction of
     IL-12 production by macrophages when stimulated in vitro with
     lipopolysaccharide or heat-killed Listeria
     monocytogenes, leading to the inhibition of the Th type 2 cytokine profile
     (decreased IL-4 and increased IFN-γ production) in antigen-primed CD4+ T
     cells.  These findings may point to a possible therapeutic use of
     berberine or medicinal plants containing berberine in the Th type 2
     cell-mediated immune diseases such as allergic diseases.

L8   ANSWER 2 OF 2  SCISEARCH  COPYRIGHT (c) 2004 The Thomson Corporation.  on
     STN
1998:795755   The Genuine Article (R) Number: 127GV. Heat-
     killed Listeria monocytogenes as an adjuvant converts
     established murine Th2-dominated immune responses into Th1-dominated
     responses.  Yeung V P; Gieni R S; Umetsu D T (Reprint); DeKruyff R H.
     STANFORD UNIV, DEPT PEDIAT, ROOM H307, STANFORD, CA 94305 (Reprint);
     STANFORD UNIV, DEPT PEDIAT, STANFORD, CA 94305. JOURNAL OF IMMUNOLOGY (15
     OCT 1998) Vol. 161, No. 8, pp. 4146-4152. Publisher: AMER ASSOC
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IMMUNOLOGISTS. 9650 ROCKVILLE PIKE, BETHESDA, MD 20814. ISSN: 0022-1767.
Pub. country: USA. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB We investigated the capacity of **heat-killed Listeria** monocytogenes (HKL), a potent stimulator of the innate immune system, as a vaccine adjuvant to modify both primary and secondary Ag-specific immune responses. Mice immunized with the Bg keyhole limpet hemocyanin (KLH) mixed with HKL generated a KLH-specific primary response characterized by production of Th1 cytokines and large quantities of KLH-specific IgG2a Ab. Moreover, administration of KLH with HKL as an adjuvant reversed established immune responses dominated by the production of Th2 cytokines and high levels of KLH-specific IgE and induced a Th1-type response with high levels of IFN-gamma and IgG2a and low levels of IgE and IL-4. Neutralization of IL-12 activity at the time of HKL administration blocked the enhancement of IFN-gamma and reduction of IL-4 production, indicating that IL-12, induced by HKL, was responsible for the adjuvant effects on cytokine production, These results suggest that HKL, as an adjuvant during immunization can successfully bias the development of Ap-specific cytokine synthesis toward Th1 cytokine production even in the setting of an ongoing Th2-dominated response. Thus, HKL may be clinically effective in vaccine therapies for diseases such as **allergy** and asthma, which require the conversion of Th2-domnated immune responses into Th1-dominated responses.

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=> s l2 and targeting
L9          56 L2 AND TARGETING

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L10          0 L9 AND FC RECEPTOR LIGAND

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PROCESSING COMPLETED FOR L9
L11          39 DUP REMOVE L9 (17 DUPLICATES REMOVED)

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L11 ANSWER 1 OF 39 CAPLUS COPYRIGHT 2004 ACS on STN
2004:857330 Document No. 141:348819 Targeted delivery of antigens in vaccines using MHC class I α3 conjugates with antibodies to cell surface markers. Zauderer, Maurice; Paris, Mark J.; Smith, Ernest S. (USA). PCT Int. Appl. WO 2004087058 A2 20041014, 115 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2004-US9385 20040326. PRIORITY: US 2003-PV457896 20030328.

AB A method of improving the efficiency of delivery of antigens for vaccine use to T cells is described. The antigen is delivered in a complex with the non-polymorphic α3 domain of a class I MHC antigen conjugated to an antibody to a cell surface marker; a β2-microglobulin, and a costimulatory mol. or cytokine. The α3 domain may be modified to improve binding to class I MHC α chains. The complexes of the invention are useful for treating and/or preventing cancer, infectious diseases, autoimmune diseases, and/or **allergies.**

L11 ANSWER 2 OF 39 CAPLUS COPYRIGHT 2004 ACS on STN
2004:802820 Document No. 141:312934 Vaccines comprising polynucleotide encoding Notch signalling modulator and antigen or antigenic determinant for medical treatment. Champion, Brian Robert; Ragno, Silvia (Lorantis Limited, UK). PCT Int. Appl. WO 2004083372 A2 20040930, 278 pp.

DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2004-GB1229 20040322. PRIORITY: GB 2003-6583 20030321; GB 2003-6582 20030321; GB 2003-6621 20030322; GB 2003-6622 20030322; GB 2003-6626 20030322; GB 2003-6624 20030322; GB 2003-6640 20030322; GB 2003-6644 20030322; GB 2003-6650 20030322; GB 2003-6651 20030322; GB 2003-6654 20030322.

AB The invention provides a particle capable of being inserted into or taken up by a cell comprising (i) a polynucleotide coding for a modulator of Notch signalling; and (ii) a polynucleotide coding for an antigen or antigenic determinant thereof. The Notch signalling modulator is Delta or Serrate/Jagged protein, fragment, derivative, homolog, analog or allelic variant. The antigen is an allergen, autoantigen, MHC antigen, or tumor antigen. The cell is immune cell, **antigen-presenting cell**, dendritic cell or Langerhans cell. Methods for using the particles are also described.

L11 ANSWER 3 OF 39 CAPLUS COPYRIGHT 2004 ACS on STN

2004:467681 Document No. 141:2405 Protein and cDNA sequences of a human toll-like receptor TLR10 and, therapeutic and diagnostic use for lymphomas. Dedera, Douglas; Emtage, Peter C. R. (Nuvelo, Inc., USA). PCT Int. Appl. WO 2004047612 A2 20040610, 87 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2003-US36971 20031119. PRIORITY: US 2002-302444 20021122; US 2002-327491 20021219; US 2003-641222 20030813.

AB **Targeting** therapy using TLR10 polypeptides, nucleic acids encoding for TLR10 polypeptides, anti-TLR10 antibodies provides a method of killing or inhibiting that growth of cancer cells that express the TLR10 protein. Methods of therapy and diagnosis of disorders associated with TLR10 protein-expressing cells are described.

L11 ANSWER 4 OF 39 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN DUPLICATE 1

2004:351228 Document No.: PREV200400352184. CTLA-4 recombinant protein genetically fused to canine Fcepsilon receptor Ialpha enhances allergen specific lymphocyte responses in experimentally sensitized dogs. Yasunaga, Sho; Tsukui, Toshihiro; Masuda, Kenichi; Ohno, Koichi [Reprint Author]; Tsujimoto, Hajime. Grad Sch Agr and Life SciDept Vet Internal MedBunkyo Ku, Univ Tokyo, 1-1-1 Yayoi, Tokyo, 1138657, Japan. Journal of Veterinary Medical Science, (June 2004) Vol. 66, No. 6, pp. 611-617. print. ISSN: 0916-7250 (ISSN print). Language: English.

AB Vaccination with a recombinant antigen fused to a **targeting** molecule is a potential strategy for inducing efficient immune responses. For the therapeutic purpose of allergic diseases in dogs, a DNA construct which expresses recombinant fusion protein with two functional domains, cytotoxic T lymphocyte antigen (CTLA-4) and Fcepsilon receptor Ialpha, was developed to bridge **antigen-presenting cells** and I-E-allergen complex. The recombinant fusion protein expressed by the DNA construct was demonstrated to retain the ability to bind monocytes in PBMC and dog IgE, respectively. Additionally, the recombinant protein induced enhancement of allergen-induced lymphoproliferation in experimentally sensitized dogs under conditions of suboptimal allergen

stimulation. These results indicated that the DNA construct could enhance allergen-induced immune responses in vivo, implying its usefulness for perspective application in immunotherapy in dogs.

L11 ANSWER 5 OF 39 CAPLUS COPYRIGHT 2004 ACS on STN
2004:603923 Document No. 141:294262 SOCS: role in inflammation, **allergy** and homeostasis. Elliott, Joanne; Johnston, James A. (Department of Microbiology and Immunology, Queen's University, Belfast, BT9 7BL, UK). Trends in Immunology, 25(8), 434-440 (English) 2004. CODEN: TIRMAE. ISSN: 1471-4906. Publisher: Elsevier Ltd..
AB A review. The suppressor of cytokine signaling (SOCS) family comprises proteins induced on cytokine stimulation, which block further signaling in a classic feedback loop. They are thought to achieve this by **targeting** signaling intermediates for degradation However, because any imbalance of these proteins can result in a broad range of pathologies, it is now clear that SOCS are also involved in determining cell fate and in regulating the inflammatory process. This occurs because each SOCS targets distinct signaling pathways, and their altered expression can cause diseases as diverse as inflammatory bowel disease, **allergy**, autoimmune diseases and diabetes. Determining the importance SOCS proteins in these human pathologies will no doubt aid the development of novel therapeutic strategies.

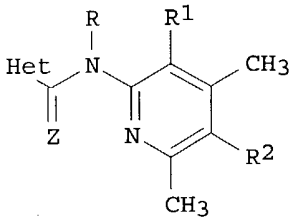
L11 ANSWER 6 OF 39 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
2004075884 EMBASE DNA vaccines for **allergy** treatment. Hartl A.; Weiss R.; Hochreiter R.; Scheiblhofer S.; Thalhamer J.. J. Thalhamer, University of Salzburg, Inst. of Chemistry and Biochemistry, Immunology Group, Hellbrunnerstr. 34, A-5020 Salzburg, Austria. Josef.Thalhamer@sbg.ac.at. Methods 32/3 (328-339) 2004. Refs: 48. ISSN: 1046-2023. CODEN: MTHDE. Pub. Country: United States. Language: English. Summary Language: English.
AB In the past 10 years, a great number of studies have demonstrated that injection of plasmid DNA coding for certain genes results in the induction of humoral and cellular immune responses against the respective gene product. This vaccination approach covers a broad range of possible applications, including the induction of protective immunity against viral, bacterial, and parasitic infections, and it opens new perspectives for treatment of cancer. Surprisingly, DNA immunization also turned out as a promising novel type of immunotherapy against **allergy.** In this paper, we describe the construction of DNA vaccines for application in **allergy** models. Beyond, we offer a palette of recently developed modulations to optimize DNA vaccines for **allergy** treatment by increasing their immunogenicity and minimizing their anaphylactic potential. .COPYRGT. 2003 Elsevier Inc. All rights reserved.

L11 ANSWER 7 OF 39 CAPLUS COPYRIGHT 2004 ACS on STN
2003:356155 Document No. 138:367601 PIR-B gene-deficient mice as model of Th2-mediated hyperimmune response for drug screening. Takai, Toshiyuki; Ujike, Azusa (Japan Science and Technology Corporation, Japan). PCT Int. Appl. WO 2003037079 A1 20030508, 50 pp. DESIGNATED STATES: W: AU, CA, US; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR. (Japanese). CODEN: PIXXD2. APPLICATION: WO 2002-JP11105 20021025. PRIORITY: JP 2001-331622 20011029.
AB It is intended to provide a nonhuman model animal of Th2-mediated hyperimmune response lacking PIR-B gene function on chromosome by which the Th2-mediated immune response mechanism and **allergy** onset mechanism in vivo can be analyzed and which is liable to suffer from not only hyper-response of B cells but also **allergy**, and an inducer/promoter or an inhibitor for Th2-mediated immune response, etc. with the use of the nonhuman model animal of Th2-mediated hyperimmune response. The nonhuman model animal of Th2-mediated hyperimmune response is prepared by integrating a fragment comprising exons 1 to 7 and the domain

in the 5' side of exon 8 of mouse PIR-B gene and another fragment containing exons 10 to 14 into a vector pMC1-Neo, cleaving it with Xho I-SalI, integrating it into a vector pIC19R-MC1tk having herpes virus thymidine kinase to thereby construct **targeting** vector, transferring the **targeting** vector into ES cells and then injecting the ES cells into blastocyst.

L11 ANSWER 8 OF 39 CAPLUS COPYRIGHT 2004 ACS on STN
2003:475477 Document No. 139:30818 Effect of benzamides compounds on the immune system and therapeutic uses as immunosuppressants. Lang, Francois; Carbonnelle, Delphine; Petit, Jean Yves; Robert, Jean Michel (Universite de Nantes, Fr.). Fr. Demande FR 2833494 A1 20030620, 34 pp. (French). CODEN: FRXXBL. APPLICATION: FR 2001-16443 20011219.

GI



I

AB The invention relates to the use of a compound of general formula (I) pour obtaining an immunosuppressor agent, in particular of an immunosuppressant **targeting** the **antigen-presenting cells** and preserving the lymphocytes T. One benzamides compound, JM-34, has been tested for its effects on T cell proliferation and cytokine production, dendritic cells maturation, mixed lymphocytes reaction and delayed type hypersensitivity. The use of those compds. for the treatment of autoimmune diseases is claimed.

L11 ANSWER 9 OF 39 CAPLUS COPYRIGHT 2004 ACS on STN
2003:77719 Document No. 138:135825 Therapeutic application of HIV-1 Tat protein. Ensoli, Barbara (Istituto Superiore di Sanita, Italy). Eur. Pat. Appl. EP 1279404 A1 20030129, 98 pp. DESIGNATED STATES: R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR. (English). CODEN: EPXXDW. APPLICATION: EP 2001-118114 20010726.

AB The author discloses vaccination, treatment, and diagnosis of HIV/AIDS and other infectious diseases, inflammatory and angiogenic diseases and tumors utilizing a biol. active HIV-1 Tat protein or fragments or derivs. thereof. The author discloses that Tat and Tat fragments can be characterized with one or more of the following features: as antigen, as adjuvant and **targeting**-delivery system to specific **antigen-presenting cells** including dendritic cells, endothelial cells and macrophages.

L11 ANSWER 10 OF 39 SCISEARCH COPYRIGHT (c) 2004 The Thomson Corporation. on STN
2003:691997 The Genuine Article (R) Number: 709CL. Hematopoietic stem cell graft manipulation as a mechanism of immunotherapy. Talmadge J E (Reprint). Univ Nebraska, Med Ctr, 600 S 42nd St, 987660, Omaha, NE 68198 USA (Reprint); Univ Nebraska, Med Ctr, Omaha, NE 68198 USA. INTERNATIONAL IMMUNOPHARMACOLOGY (AUG 2003) Vol. 3, No. 8, pp. 1121-1143. Publisher: ELSEVIER SCIENCE BV. PO BOX 211, 1000 AE AMSTERDAM, NETHERLANDS. ISSN: 1567-5769. Pub. country: USA. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Hematopoietic stem cell transplants (SCT) are used in the treatment of

neoplastic diseases, in addition to congenital, autoimmune, and inflammatory disorders. Both autologous and allogeneic SCT are used, depending on donor availability and the type of disease being treated, resulting in different morbidity and outcomes. In both types of SCT, immune regulation via graft manipulation is being studied, although with highly different targeted outcomes. In general, autologous SCT have lower treatment-related morbidity and mortality, but a higher incidence of tumor relapse, and graft manipulation targets immune augmentation and/or the reduction of immune tolerance. In contrast, allogeneic SCT have a higher incidence of treatment-related morbidity and mortality and a significantly longer time of disease progression, and the targeted outcomes or graft manipulation focus on a reduction in graft versus host disease (GVHD). One source of the increased relapse rate and shorter overall survival (OS) following high dose chemotherapy (HDT) and autologous SCT is the immune tolerance that limits host response, both innate and antigen (Ag) specific, against the tumor. The immune tolerance that is observed is due in part to the tumor burden and prior cytotoxic therapy. Therefore, graft manipulation, as an adjuvant therapeutic approach in autologous SCT, is primarily focused on non-specific or specific immune augmentation using cytokines and vaccines. Recently, manipulation of the infused product as a form of cellular therapy has begun to also focus on approaches to reduce immune tolerance found in transplant patients, both prior to and following HDT and SCT. To this end, graft manipulation to reduce the presence of Fas Ligand (FasL)-expressing cells or interleukin (IL)10 and tumor growth factor (TGF)beta production has been proposed.

In contrast to autologous transplantation, graft manipulation during allogeneic transplantation is used extensively. This includes limiting the infusion of T cells within the product or as a donor leukocyte infusion (DLI), resulting in a reduction in GVHD and the induction of long-term survivors. Indeed, allogeneic SCT provide the only curative therapy for patients with chronic myelogenous leukemia (CML), refractory acute leukemia, and myelodysplasia. The curative potential of allogeneic SCT is reduced, however, by the development of GVHD, a potentially lethal T-cell-mediated immune response **targeting** host tissues [Int. Arch. **Allergy** Immunol. 102 (1993) 309, J. Exp. Med. 183 (1996) 589]. The morbidity and mortality associated with GVHD limit this technology, resulting focus on those patients who have no alternative therapeutic options or who have advanced disease. Thus, allogeneic SCT provide one of the few statistically supported demonstrations of therapeutic efficacy by T cells (comparison of allogeneic to autologous transplantation). In contrast to autologous transplantation, control of GVHD following allogeneic SCT focuses on immune suppression and the induction of tolerance. Here too, graft manipulation is appropriate, and there are numerous studies of T-cell depletion to reduce GVHD, with or without the isolation and infusion of T cells as DLI. Additional strategies are examining the isolation and infusion of T cells with graft versus leukemia (GVL) activity to reduce GVHD and/or the infusion of genetically manipulated and/or selected cellular populations (monocytes or dendritic cells (DC)) to induce tolerance.

Therefore, depending upon the type of transplant, the goals associated with graft manipulation can be radically different. In this review, we emphasize using graft manipulation to regulate immune tolerance and anergy in association with SCT. Although this paper focuses on hematopoictic SCT, it should be noted that these strategies are relevant to conditions other than neoplastic and congenital diseases, including solid organ transplants, and autoimmune and inflammatory diseases.

L11 ANSWER 11 OF 39 EMBASE
on STN

2003122155 EMBASE The role of T lymphocytes in the pathogenesis of asthma. Larche M.; Robinson D.S.; Kay A.B.. Dr. A.B. Kay, Dept. of Allerg./Clinical Immunology, National Heart and Lung Institute, Imperial College London, Dovehouse St, London SW3 6LY, United Kingdom. Journal of Allergy and Clinical Immunology 111/3 (450-463) 1 Mar 2003.

Refs: 145.
ISSN: 0091-6749. CODEN: JACIBY. Pub. Country: United States. Language: English. Summary Language: English.

AB There is considerable evidence to support a role for T cells in asthma, particularly the involvement of T(H)2 cells both in atopic allergic asthma and in nonatopic and occupational asthma. There might also be a minor contribution from T(C)2 CD8(+) T cells. Several T(H)2 cytokines have the potential to modulate airway inflammation, particularly IL-13, which induces airway hyperresponsiveness independently of IgE and eosinophilia in animal models. The identification of transcription factors controlling T(H)1 and T(H)2 development further support the T(H)2 hypothesis because GATA3 is overexpressed and T-bet is underexpressed in the asthmatic airway. Specific T cell-directed immunotherapy might allow induction, modulation, or both of T-cell responses, and elucidation of the mechanisms of regulatory T cells might allow further optimization of immunotherapy. Recent advances in our understanding of dendritic cell function in directing T-cell responses might uncover further therapeutic targets. The efficacy of cyclosporin A and anti-CD4 treatment in patients with chronic severe asthma argues for continued T-cell involvement, but whether remodeling contributes to pathology inaccessible to anti-inflammatory treatment or T-cell immunotherapy will be an important future question.

L11 ANSWER 12 OF 39 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN DUPLICATE 2

2003:587355 Document No.: PREV200300587889. Advances in immunological treatment of **allergy**. Kussebi, F.; Karamloo, F.; Akdis, M.; Blaser, K.; Akdis, C. [Reprint Author]. Swiss Institute of Allergy and Asthma Research (SIAF), Obere Strasse 22, CH-7270, Davos, Switzerland. akdisac@siaf.unizh.ch. Current Medicinal Chemistry - Anti-Inflammatory & Anti-Allergy Agents, (December 2003) Vol. 2, No. 4, pp. 297-308. print. ISSN: 1568-0142 (ISSN print). Language: English.

L11 ANSWER 13 OF 39 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

2004295163 EMBASE Lessons from drug **allergy**: Against dogmata. Pichler W.J.. Dr. W.J. Pichler, Div. of Allergol. Clin. of Rheumatol, Inselspital, University of Bern, 3010 Bern, Switzerland. werner.pichler@insel.ch. Current Allergy and Asthma Reports 3/1 (1-3) 2003.
Refs: 22.
ISSN: 1529-7322. Pub. Country: United Kingdom. Language: English.

L11 ANSWER 14 OF 39 CAPLUS COPYRIGHT 2004 ACS on STN

2002:793359 Document No. 137:293546 Chimeric immunogens targeted to endosomal/lysosomal compartments. August, Thomas; Marques, Ernesto, Jr. (The Johns Hopkins University, USA). PCT Int. Appl. WO 2002080851 A2 20021017, 102 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-US10757 20020405. PRIORITY: US 2001-PV281607 20010405; US 2001-PV281608 20010405; US 2001-PV281621 20010405.

AB The authors disclose chimeric proteins comprising an antigen sequence and a domain for trafficking the protein to an endosomal compartment, irresp. of whether the antigen is derived from a membrane or non-membrane protein. In one preferred aspect, the trafficking domain comprises a lumenal domain of a LAMP polypeptide. Alternatively, or addnl., the chimeric protein comprises a trafficking domain of an endocytic receptor (e.g., such as DEC-205 or gp200-MR6). In one example, immune responses to a p55Gag DNA vaccine was enhanced for a construct comprising the Gag protein fused

N-terminal to the LAMP-1 protein.

L11 ANSWER 15 OF 39 CAPLUS COPYRIGHT 2004 ACS on STN
2002:449521 Document No. 137:37617 Immunomodulatory constructs and their uses. Fraser, John David; Nicholson, Melissa Joy (Auckland Uniservices Limited, N. Z.). PCT Int. Appl. WO 2002045739 A1 20020613, 47 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-NZ267 20011204. PRIORITY: US 2000-PV251243 20001204.
AB An immunomodulator which comprises an **antigen-presenting -cell** (APC)-**targeting** mol. coupled to an immunomodulatory antigen is disclosed, wherein said APC-**targeting** mol. mimics a superantigen but does not include a fully functional T-cell receptor binding site.

L11 ANSWER 16 OF 39 CAPLUS COPYRIGHT 2004 ACS on STN
2002:184921 Document No. 136:246375 Down-regulation of IgE by vaccination. Klysner, Steen; Von Hoegen, Paul; Voldborg, Bjorn; Gautam, Anand (Pharmexa A/S, Den.). PCT Int. Appl. WO 2002020038 A2 20020314, 151 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, CZ, DE, DE, DK, DK, DM, DZ, EC, EE, EE, ES, FI, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-DK579 20010906. PRIORITY: DK 2000-1326 20000906; US 2000-PV232831 20000915.
AB The authors disclose methods for immunizing against autologous (self) IgE. In particular, the invention discloses methods for inducing cytotoxic T-lymphocytes to B-cells producing autologous IgE. Vaccination may be administered by nucleic acid vaccination or live vaccination. Also disclosed are methods for inducing antibodies reactive with autologous IgE as well as methods for inducing a combined antibody and CTL response specific for IgE.

L11 ANSWER 17 OF 39 MEDLINE on STN DUPLICATE 3
2002700232. PubMed ID: 12417885. High-level expression of immunoreactive recombinant cat allergen (Fel d 1): **Targeting** to **antigen -presenting cells.** Vailes Lisa D; Sun Amanda W; Ichikawa Kunio; Wu Zining; Sulahian Timothy H; Chapman Martin D; Guyre Paul M. (INDOOR Biotechnologies Inc, Charlottesville, VA 22903, USA.) Journal of allergy and clinical immunology, (2002 Nov) 110 (5) 757-62. Journal code: 1275002. ISSN: 0091-6749. Pub. country: United States. Language: English.
AB BACKGROUND: Cat allergen Fel d 1 is a heterodimer encoded by 2 separate genes that has been difficult to produce as a fully immunoreactive molecule. OBJECTIVE: We sought to engineer recombinant (r) Fel d 1 with IgE and IgG antibody binding comparable with that of the natural allergen that could be targeted to **antigen-presenting cells.** METHODS: The rFel d 1 chains were coexpressed in baculovirus, either linked to the anti-CD64 antibody H22 (rFel d 1 H22(+)) or alone (rFel d 1 H22 (-)). Binding of expressed allergens to mouse and human antibodies was compared with that of natural (n) Fel d 1 by means of enzyme immunoassay and antigen-binding and inhibition RIAs. Binding of rFel d 1 H22 (+) to the CD64 receptor on leukocyte subpopulations and on the THP -1 cell line was analyzed by means of flow cytometry. RESULTS: The baculovirus-expressed allergens migrated with molecular weights of 49

kd (rFel d 1 H22(+)) and 22 kd (rFel d 1 H22 (-)). The rFel d 1 inhibited IgG antibody binding to nFel d 1 by greater than 95% and showed identical dose-dependent inhibition curves. There was an excellent quantitative correlation between IgE and IgG antibody binding to rFel d 1 and nFel d 1 in sera from patients with cat **allergy** (IgE: n = 258, r = > 0.72,P <.001). The rFel d 1 H22(+) bound to monocytes but not to lymphocytes or neutrophils, and binding of rFel d 1 H22(+) to THP-1 cells was inhibited by a soluble CD64 fusion protein. CONCLUSIONS: Recombinant Fel d 1 chains have been successfully coexpressed as mature proteins with comparable immunoreactivities to nFel d 1. The rFel d 1 can be targeted to **antigen-presenting cells** through CD64.
These constructs will facilitate structural studies of Fel d 1 and the development of improved **allergy** diagnostics and therapeutics.

L11 ANSWER 18 OF 39 MEDLINE on STN DUPLICATE 4
2002145033. PubMed ID: 11842304. Scavenger receptor-specific allergen delivery elicits IFN-gamma-dominated immunity and directs established TH2-dominated responses to a nonallergic phenotype. Bhatia Sumeena; Mukhopadhyay Sangita; Jarman Elizabeth; Hall Gillian; George Anna; Basu Sandip K; Rath Satyajit; Lamb Jonathan R; Bal Vineeta. (National Institute of Immunology, New Delhi, India.) Journal of allergy and clinical immunology, (2002 Feb) 109 (2) 321-8. Journal code: 1275002. ISSN: 0091-6749. Pub. country: United States. Language: English.
AB BACKGROUND: Immunotherapeutic approaches to **allergy** consist of reliably changing allergen-specific T(H)2 immunity associated with secretion of IL-4, IL-5, and IL-13, along with IgE antibodies in atopic individuals to T(H)1 immunity. Our earlier data show that **targeting** of protein antigens to **antigen-presenting cells** (APCs), such as macrophages, by means of scavenger receptors (SRs) results in a pronounced T(H)1 immunity. Here we demonstrate a novel experimental approach for the conversion of T(H)2 immunity to T(H)1 immunity by using SR delivery of allergens. OBJECTIVES: We sought to show that **targeting** of allergens by means of SRs to APCs triggers T(H)1 immunity and that an established T(H)2 immunity to the Der p 1-immunodominant peptide 111-139 (p1, 111-139) can be modulated to a nonallergic T(H)1 phenotype. METHODS: Analysis of the T cell-derived cytokines IL-4, IL-5, IL-13, and IFN-gamma in response to p1, 111-139 in C57BL/6 mice 7 to 42 days after immunization, measurement of specific antibody responses, eosinophilic infiltrate, and skin hypersensitivity in response to allergen challenge constitute the parameters of in vivo immunity. RESULTS: We show that p1, 111-139, when delivered to APCs by means of SR, elicits a T(H)1-dominant immunity. If it is delivered to APCs either after chemical coupling to SR ligands or by means of mere coadsorption on alum in the presence of an SR ligand, the established T(H)2 immunity can be modified to T(H)1 immunity. CONCLUSIONS: SR-mediated delivery of allergens has immunotherapeutic potential that may be usable in atopic individuals.

L11 ANSWER 19 OF 39 CAPLUS COPYRIGHT 2004 ACS on STN
2002:838709 Document No. 138:135278 Immunostimulatory DNA for allergic asthma. Ikeda, Reid K.; Takabayashi, Kenji; Broide, David (Department of Medicine, University of California at San Diego, La Jolla, CA, USA). Microbial DNA and Host Immunity, 289-299. Editor(s): Raz, Eyal. Humana Press Inc.: Totowa, N. J. ISBN: 1-58829-022-0 (English) 2002. CODEN: 69DFSH.
AB A review discusses mechanisms of action and potential efficacy of DNA-based approach, with emphasis on the immunostimulatory sequence (ISS)-protein allergen conjugate therapy, in the treatment of asthma. Exon-coding DNA vaccines are designed to inhibit T helper 2 (Th2) immune response to specific DNA encoded allergens. ISS therapy redirects the host immune response from Th2 to a Th1 response. ISS-allergen protein conjugate therapy improves the efficacy of unconjuagated ISS therapy by **targeting** ISS and the protein allergen to the same **antigen-presenting cell.**

L11 ANSWER 20 OF 39 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

2003192722 EMBASE Needle-free epidermal powder immunization. Chen D.; Maa Y.-F.; Haynes J.R.. D. Chen, PowderJect Vaccines Inc., 585 Science Drive, Madison, WI 53711, United States. dexiang_chen@powderject.com. Expert Review of Vaccines 1/3 (265-276) 2002.
Refs: 78.
ISSN: 1476-0584. CODEN: ERVXAX. Pub. Country: United Kingdom. Language: English. Summary Language: English.

AB Due to the presence of a network of **antigen-presenting cells** and other cells with innate and adaptive immune functions, the skin is both a sensitive immune organ and a practical target site for vaccine administration. A handful of needle-free immunization technologies have emerged in recent years that aim to take advantage of these characteristics. Skin delivery technologies provide potentially safer alternatives to needle injection and promises increased efficacy in the prevention and/or therapy of infectious diseases, allergic disorders and cancer. In this review, we will cover advances in needle-free skin vaccination technologies and their potential applications to disease prevention and therapy. Emphasis will be placed on epidermal powder immunization and particle-mediated ('gene gun') DNA immunization, which use similar mechanical devices to deliver protein and DNA vaccines, respectively, into the viable epidermis.

L11 ANSWER 21 OF 39 MEDLINE on STN DUPLICATE 5

2002393974. PubMed ID: 12141986. Strategies for designing vaccines eliciting Th1 responses in humans. Moingeon P. (Research and Development, Aventis Pasteur, Campus Merieux, 1541 Avenue Marcel Merieux, 69280 Marcy L'Etoile, France.. philippe.moingeon@aventis.com) . Journal of biotechnology, (2002 Sep 25) 98 (2-3) 189-98. Ref: 64. Journal code: 8411927. ISSN: 0168-1656. Pub. country: Netherlands. Language: English.

AB There is currently a major interest in designing vaccines capable of eliciting strong cellular immune responses. The induction of cytotoxic and Th1 helper cellular responses is for example highly desirable for vaccines **targeting** either chronic infectious diseases or cancers (therapeutic vaccines). Similarly, Th1 vaccines would be useful in redirecting inappropriate antigen-specific immune responses in patients with autoimmune diseases and **allergies.** Importantly, emerging technologies and a better understanding of the physiology of immune responses offer new avenues to rationally design such vaccines. Approaches based on the identification and selection of immunogens containing T cell epitopes can be used, together with epitope-enhancement strategies, to increase binding to MHC, or to improve recognition by T cell receptor complexes. Optimized immunogens can subsequently be presented to the immune system with appropriate vectors allowing to target professional **antigen-presenting cells**, such as dendritic cells. Such antigen presentation platforms can be used alone or in association, as part of mixed immunization regimens (heterologous prime-boosts), in order to elicit broad immune responses. The rational design of Th1 adjuvants can also benefit from our better understanding of the nature of proinflammatory signals leading to the initiation of both innate and adaptive immune effector mechanisms. Candidate Th1 vaccines (or components such as vectors or adjuvants) will have to be tested in exploratory clinical studies, implying a need for new assays and methods allowing to assess in a qualitative and quantitative manner low-frequency T cell responses in humans.

L11 ANSWER 22 OF 39 MEDLINE on STN DUPLICATE 6

2002373244. PubMed ID: 12118944. **Targeting** epidermal Langerhans cells by epidermal powder immunization. Chen Dexiang; Payne Lendon G. (PowderJect Vaccines, Inc., Madison, WI 53711, USA.. dexiang_chen@powderject.com) . Cell research, (2002 Jun) 12 (2) 97-104. Ref: 50. Journal code: 9425763. ISSN: 1001-0602. Pub. country: China. Language: English.

AB Immune reactions to foreign or self-antigens lead to protective immunity

and, sometimes, immune disorders such as **allergies** and autoimmune diseases. **Antigen presenting cells** (APC) including epidermal Langerhans cells (LCs) play an important role in the course and outcome of the immune reactions. Epidermal powder immunization (EPI) is a technology that offers a tool to manipulate the LCs and the potential to harness the immune reactions towards prevention and treatment of infectious diseases and immune disorders.

L11 ANSWER 23 OF 39 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
2002407660 EMBASE Today's science - Tomorrow's practice: Basic mechanisms of **allergy** and their clinical implications. Holgate S.T.. S.T. Holgate, Infect., Inflammation/Repair Div., University of Southampton, Southampton General Hospital, Southampton SO16 6YD, United Kingdom. s.holgate@soton.ac.uk. Clinical and Experimental Allergy Reviews 2/1 (48-54) 2002.
Refs: 41.
ISSN: 1472-9725. CODEN: CEARC3. Pub. Country: United Kingdom. Language: English. Summary Language: English.
AB The current therapeutic perspective for the treatment of allergic disorders has shifted from mediators of **allergy**, such as histamine, to focus on cytokines and their interactions with cells involved in allergic inflammation. Although eosinophils are involved in the genesis of **allergy** in animal models, their role in human asthma has been questioned. On the other hand, immunoglobulin E (IgE) appears to play a key role in allergic reactions and is therefore the focus of therapeutic attention. Similarly, the relationship between allergic reactions and T-helper 1 (Th1) and Th2 cells has been the subject of intensive investigation. In addition to the inflammation that characterizes the allergic response, there are structural changes in the airways that may precede any obvious clinical disease. These structural changes, affecting the epithelial-mesenchymal trophic unit, may in part be genetically determined and will require treatment at the molecular biological level.

L11 ANSWER 24 OF 39 CAPLUS COPYRIGHT 2004 ACS on STN
2001:780722 Document No. 135:348863 Targeted vaccine delivery systems. Zauderer, Maurice; Smith, Ernest S. (University of Rochester, USA). PCT Int. Appl. WO 2001078768 A2 20011025, 167 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2001-US11912 20010412. PRIORITY: US 2000-PV196472 20000412.
AB The present invention is directed to a novel targeted vaccine delivery system, comprising one or more MHC-peptide complexes linked to an antibody which is specific for a cell surface marker. The complexes of the invention are useful for treating and/or preventing cancer, infectious diseases, autoimmune diseases, and/or **allergies.**

L11 ANSWER 25 OF 39 CAPLUS COPYRIGHT 2004 ACS on STN
2001:208317 Document No. 134:251191 Dendritic cell membrane protein CIRE. Caminschi, Irina; Wright, Mark Dexter; Shortman, Kenneth Douglas (The Council of the Queensland Institute of Medical Research, Australia). PCT Int. Appl. WO 2001019869 A1 20010322, 53 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA,

GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-AU1096 20000913. PRIORITY: AU 1999-2788 19990913.

AB The present invention relates to a type II integral membrane protein of 238 amino acids (designated CIRE) which is preferentially expressed in dendritic cells, macrophages and their precursors stimulatory to T cells, nucleic acid sequences encoding this protein and antibodies. The ligands of the present invention may be used to isolate dendritic cells or precursors, to modulate immune responses (therefore to treat **allergy** and autoimmune disease, or to prevent viral or bacterial infection), or to target mol. (e.g. vaccine) to dendritic or **antigen presenting cells.** The invention also relates to uses of the protein, nucleic acids and antibodies in screening compds. for immunol. regulating activity and for modulating an immune response.

L11 ANSWER 26 OF 39 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

2001433034 EMBASE IL-1α, but not IL-1B, is required for contact-allergen-specific T cell activation during the sensitization phase in contact hypersensitivity. Nakae S.; Naruse-Nakajima C.; Sudo K.; Horai R.; Asano M.; Iwakura Y.. Y. Iwakura, Center for Experimental Medicine, Institute of Medical Science, University of Tokyo, 4-6-1 Shirokanedai, Minato-ku, Tokyo 108-8639, Japan. International Immunology 13/12 (1471-1478) 2001.
Refs: 38.
ISSN: 0953-8178. CODEN: INIMEN. Pub. Country: United Kingdom. Language: English. Summary Language: English.

AB Contact hypersensitivity (CHS) is a T cell-mediated cellular immune response caused by epicutaneous exposure to contact allergens. In this reaction, after the first epicutaneous allergen sensitization, Langerhans cells (LC) catch allergens and migrate from the skin to draining lymph nodes (LN) and activate naive T cells. Although IL-1 is suggested to be involved in these processes, the mechanisms have not been elucidated completely. In this report, to elucidate roles of IL-1α and IL-1β in CHS, we analyzed ear swelling in 2,4,6-trinitrochlorobenzene (TNCB)-induced CHS using gene-targeted mice. We found that ear swelling was suppressed in IL-1α-deficient (IL-1α(-/-)) mice but not in IL-1β(-/-) mice. LC migration from the skin into LN was delayed in both IL-1α(-/-) and IL-1β(-/-) mice, suggesting that this defect was not the direct cause for the reduced CHS in these mice. However, we found that the proliferative response of trinitrophenyl (TNP)-specific T cells after sensitization with TNCB was specifically reduced in IL-1α(-/-) mice. Furthermore, adoptive transfer of TNP-conjugated IL-1-deficient epidermal cells (EC) into wild-type mice indicated that only IL-1α, but not IL-1β, produced by **antigen-presenting cells** in EC could prime allergen-specific T cells. These observations indicate that IL-1α, but not IL-1β, plays a crucial role in TNCB-induced CHS by sensitizing TNP-specific T cells.

L11 ANSWER 27 OF 39 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

2001173273 EMBASE Effective antigen presentation by dendritic cells is NF-κB dependent: Coordinate regulation of MHC, co-stimulatory molecules and cytokines. Yoshimura S.; Bondeson J.; Foxwell B.M.J.; Brennan F.M.; Feldmann M.. M. Feldmann, Kennedy Inst. Rheumatology Division, Imperial College School of Medicine, 1 Aspenlea Road, Hammersmith, London W6 8LH, United Kingdom. International Immunology 13/5 (675-683) 2001.
Refs: 55.
ISSN: 0953-8178. CODEN: INIMEN. Pub. Country: United Kingdom. Language: English. Summary Language: English.

AB Antigen presentation is a key rate-limiting step in the immune response. Dendritic cells (DC) are the most potent **antigen-**

presenting cells for naive T cells, due to their high expression of MHC and co-stimulatory molecules, but little is known about the biochemical pathways that regulate this function. We here demonstrate that monocyte-derived mature DC can be infected with adenovirus at high efficiency (>95%) and that this procedure can be used to dissect out which pathways are essential for inducing DC antigen presentation to naive T cells. Using adenoviral transfer of the endogenous inhibitor of NF-κB, IκBα, we show that DC antigen presentation is NF-κB dependent. The mechanism for this is that NF-κB is essential for three aspects of antigen-presenting function: blocking NF-κB coordinately down-regulates HLA class II, co-stimulatory molecules like CD80, CD86 and CD40, and immuno-stimulatory cytokines like IL-12 and tumor necrosis factor-α. In contrast adhesion molecules are up-regulated after infection with the adenovirus transferring IκBα, indicating that NF-κB also regulates the duration of T cell-DC interaction. These results establish NF-κB as an effective target for blocking DC antigen presentation and inhibiting T cell-dependent immune responses, and this finding has potential implications for the development of therapeutic agents for use in **allergy**, autoimmunity and transplantation.

L11 ANSWER 28 OF 39 CAPLUS COPYRIGHT 2004 ACS on STN
2000:883471 Document No. 135:44823 Principles of genetic immunization. Lee, D. J.; Takabayashi, K.; Corr, M.; Raz, E. (Department of Medicine, University of California, La Jolla/San Diego, CA, 92093-0663, USA). Skin and Gene Therapy, 177-200. Editor(s): Hengge, Ulrich R.; Volc-Platzer, Beatrix. Springer-Verlag: Berlin, Germany. (English) 2001. CODEN: 69ASR6.

AB A review with 114 refs. Using plasmids to express protein antigens in vivo has opened many opportunities in the areas of vaccination against infectious diseases, **allergy**, and cancer immunotherapy. While the initial expts. showing in vivo expression were performed in muscle, similar results have been obtained in the skin. **Targeting** the skin has allowed DNA vaccines (also known as gene vaccines, genetic vaccines, or DNA immunization) to take advantage of the abundance of **antigen-presenting cells** in the skin.
Although there are several advantages to the use of plasmid DNA vaccination, some disadvantages will be described as well. Most importantly, DNA immunization results in very strong cell mediated immune responses. While immunostimulatory sequences (ISS) present in the plasmid are required, the mechanism by which DNA vaccines induce these potent immune responses are still not fully elucidated. This review will discuss these various aspects of genetic immunization in greater detail.

L11 ANSWER 29 OF 39 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
2001277434 EMBASE **Targeting** the allergen-specific CD4(+) T cell - Strategies for improved allergen immunotherapy. Rolland J.; O'Hehir R.E.. R. O'Hehir, Dept. Allergy Asthma/Clin. Immunol., The Alfred and Monash University, Commercial Road, Prahran, Vic. 3181, Australia. Robyn.Ohehir@med.monash.edn.au. Allergy and Clinical Immunology International 13/4 (170-177) 2001.
Refs: 66.
ISSN: 0838-1925. CODEN: ACIIFH. Pub. Country: Switzerland. Language: English. Summary Language: English.

AB Background: Clinically effective specific immunotherapy (SIT) for **allergy** is associated with an altered T-cell response to allergen. In particular, the proliferative response and interleukin-4 (IL-4) production are decreased. Interferon γ (IFN-γ) production is increased with insect venom SIT, but with aeroallergens variable effects on IFN-γ production are observed. Mechanisms proposed to explain these findings are anergy, deletion, and immune deviation. Therefore, new strategies for SIT can be devised based on **targeting** the allergen-specific T-cell response. Methods/data base: Studies on factors which influence the outcome of T-cell interaction with its specific ligand

and the role of these factors in controlling the T-cell response to an allergen are reviewed. Results: The physical and chemical nature of an allergen, the concentration of allergen, the use of adjuvant, and the route of administration have all been shown to influence the degree and type of T-cell response. Mechanisms by which these variables influence T-cell response are being elucidated. Conclusions: More effective SIT can be achieved by **targeting** the allergen-specific CD4+ T cell using allergen preparations such as peptides based on dominant T-cell epitopes and mutant allergens where immunoglobulin E (IgE)-binding sites have been abrogated but T-cell reactive sites retained. These treatments will also be safer since they will fail to cross-link mast-cell-bound IgE. Elucidation of factors associated with the form of an allergen, its concentration and the **antigen-presenting cell** type and activation state will permit further refinement of SIT regimens for treatment of allergic diseases.

L11 ANSWER 30 OF 39 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

2001254861 EMBASE Current reviews of **allergy** and clinical immunology: Alternative agents in asthma. Frew A.J.; Plummeridge M.J.. Dr. A.J. Frew, Mailpoint 810, Southampton General Hospital, Southampton SO16 6YD, United Kingdom. Journal of Allergy and Clinical Immunology 108/1 (3-10) 2001.
Refs: 82.
ISSN: 0091-6749. CODEN: JACIBY. Pub. Country: United States. Language: English. Summary Language: English.

AB Glucocorticosteroids are the backbone of asthma therapy and are administered mainly by the inhaled route. Patients with "difficult" asthma are not a single homogeneous group. Some are stable on high-dose steroid therapy but experience unacceptable side effects; others remain unstable despite receiving high doses of inhaled or oral steroids. Several different steroid-sparing and alternative agents have been tried, with varying degrees of success. Some success has been achieved with conventional immunosuppressants such as methotrexate, gold, and cyclosporin A, but these agents can be justified only in a limited range of cases. Leukotriene receptor antagonists have proved a useful addition to asthma therapy and have been shown to have a modest steroid-sparing effect. Although the existing range of alternative agents has not proved to be particularly effective, several new therapeutic agents have been developed to target specific components of the inflammatory process in asthma. These include IgE antibodies, cytokines, chemokines, and vascular adhesion molecules. Future developments might include better forms of immunotherapy and strategies **targeting** the remodeling of structural elements of the airways.

L11 ANSWER 31 OF 39 CAPLUS COPYRIGHT 2004 ACS on STN

2000:741936 Document No. 133:308997 Methods for skewing the balance between Th1 and Th2 immune responses. Bottomly, H. Kim; Caplan, Michael J.; Sosin, Howard B. (Panacea Pharmaceuticals, LLC, USA). PCT Int. Appl. WO 2000061157 A1 20001019, 76 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US9270 20000407. PRIORITY: US 1999-290029 19990409.

AB The present invention provides compns. and methods for regulating immune system reactions by biasing T cell responses away from Th1 or Th2 responses in a pre-determined manner. Control is effected at the stage of antigen/APC encounter and/or at the stage of APC/T cell encounter. In preferred embodiments, a Th1 or Th2 response is inhibited through induction of the alternative response. The inventive methods and reagents are particularly useful for the management of autoimmune disorders,

allergy, and asthma.

L11 ANSWER 32 OF 39 CAPLUS COPYRIGHT 2004 ACS on STN
2000:335272 Document No. 132:352759 Use of an OmpA outer membrane protein of an enterobacterium for specific **targeting** of drugs to **antigen-presenting cells.** Bonnefoy, Jean-Yves; Lecoanet, Sybille; Aubry, Jean-Pierre; Jeannin, Pascale; Baussant, Thierry (Pierre Fabre Medicament, Fr.). PCT Int. Appl. WO 2000027432 A1 20000518, 35 pp. DESIGNATED STATES: W: AU, BR, CA, CN, JP, MX, US, ZA; RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE. (French). CODEN: PIXXD2. APPLICATION: WO 1999-FR2734 19991108. PRIORITY: FR 1998-14007 19981106.
AB The invention concerns the use of an enterobacterium protein OmpA, preferably Klebsiella pneumoniae P40 protein, for specific **targeting** of a biol. active substance associated therewith towards **antigen-presenting cells**, in particular human dendritic cells. The invention also concerns the use of the OmpA protein for preparing a pharmaceutical composition for preventing and/or treating diseases, in particular cancers related to a tumor-associated antigen, autoimmune diseases or infectious diseases. The protein can be manufactured as inclusion bodies in Escherichia coli and purified chromatog. after solubilization. Alexa 488-labeled K. pneumoniae OmpA (p40) showed specific, dose-dependent binding to dendritic cells. Other possible carrier proteins, such as tetanus toxins and protein G derivs. did not bind dendritic cells. P40 is also internalized by dendritic cells.

L11 ANSWER 33 OF 39 CAPLUS COPYRIGHT 2004 ACS on STN
2000:14955 Document No. 132:77618 Methods and compositions for modulating antigen-specific immunological (humoral) responses by **targeting** such antigen to APCs in conjunction with anti-CD40 ligand administration. Wade, William F.; Demian, Douglas (Trustees of Dartmouth College, USA). PCT Int. Appl. WO 2000000156 A2 20000106, 46 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 1999-US12825 19990625. PRIORITY: US 1998-90849 19980626.
AB Methods and compns. are provided which upon administration to a subject in need of such treatment result in enhanced or suppressed immunol. responses and in particular enhanced or suppressed humoral (antibody) immune responses to a desired antigen. These methods and compns. include an antigen directly or indirectly attached to an antibody specific for antigen expressed by an **antigen-presenting cell** and optionally an anti-CD40 antibody. These methods and compns. are particularly useful in the treatment of infectious diseases, such as viral, bacterial or fungal infection, and the treatment and/or prevention of cancer, especially for treatment of aged individuals or other subjects having impaired immune systems, and the treatment of autoimmune diseases, transplant, **allergy**, inflammatory diseases, wherein suppression of antigen-specific immune response is therapeutically beneficial.

L11 ANSWER 34 OF 39 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
2001020481 EMBASE **Targeting** cytokines in asthma therapy: Round one.
Boushey A.H.; Fahy J.V.. A.H. Boushey, Department of Medicine, Univ. of California San Francisco, San Francisco, CA 94143, United States. Lancet 356/SUPPL. (2114-2116) 2000.
Refs: 11.
ISSN: 0140-6736. CODEN: LANCAO. Pub. Country: United Kingdom. Language: English.

L11 ANSWER 35 OF 39 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN DUPLICATE 7

1997:250351 Document No.: PREV199799549554. IgE-mediated allergen presentation via Fc epsilon RI on **antigen-presenting cells**. Stingl, Georg [Reprint author]; Maurer, Dieter. Div. Immunol., Allergy Infectious Diseases, Dep. Dermatol., Univ. Vienna Med. Sch., Waehringer Guertel 18-20, A-1090 Vienna, Austria. International Archives of Allergy and Immunology, (1997) Vol. 113, No. 1-3, pp. 24-29.
CODEN: IAAIEG. ISSN: 1018-2438. Language: English.

AB In atopic individuals, cutaneous **antigen-presenting cells** (APC), i.e., Langerhans' cells (LC) and dermal dendritic cells (DDC), frequently display anti-IgE reactivity. While earlier observations suggested that this phenomenon results from the binding of (complexed) IgE to the low affinity IgE receptor (Fc-epsilon-RII/CD23), recent evidence exists that LC and DDC, as well as peripheral blood dendritic cells and monocytes from atopic individuals, can bind monomeric IgE via the high-affinity receptor for IgE (Fc-epsilon-RI). We have now found that Fc-epsilon-RI, both quantitatively and qualitatively, is the pivotal serum IgE-binding structure on APC of atopic individuals, that Fc-epsilon-RI on APC functions as allergen-focusing molecule and that allergens are more efficiently taken up, processed and presented to T cells following **targeting** to APC via Fc-epsilon-RI compared to allergen binding to APC in the conventional manner. In vivo, Fc-epsilon-RI-IgE-dependent allergen presentation may critically lower atopic individuals' threshold to mount allergen-specific T cell responses. This would result in the perpetuation of allergen-specific IgE production (type I reactions) and perhaps even in the occurrence of T-cell-mediated delayed-type hypersensitivity reactions in allergen-exposed tissues.

L11 ANSWER 36 OF 39 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN DUPLICATE 8

1997:37245 Document No.: PREV199799329233. Allergen-specific Th2 cells as targets for immune intervention in allergic disease. De Vries, Jan E.. Human Immunol. Dep., DNAX Research Inst. Molecular Cellular Biol., 901 California Ave., Palo Alto, CA 94304-1104, USA. Allergology International, (1996) Vol. 45, No. 3, pp. 117-123.
ISSN: 1323-8930. Language: English.

AB Allergen-specific Th2 cells from atopic individuals generally belong to the T helper 2 (Th2) subset producing, among other cytokines, high levels of IL-4, IL-5 and IL-13, but low levels of IL-2 and IFN-gamma following activation. Both IL-4 and IL-13 induce IgE synthesis, which is inhibited by IFN-gamma. IL-4, but not IL-13, also directs differentiation of naive CD4+ T cells into Th2 cells. Furthermore, IL-5 induces the differentiation of eosinophils and eosinophilia, whereas IL-3, IL-4 and IL-10 produced by Th2 cells, synergize with c-kit ligand in promoting most cell growth. These observations indicate that **allergy** is a Th2 cell disease, and that **targeting** of allergen-specific Th2 cells may provide an efficient way to intervene in allergic inflammation. Three different approaches aimed at inhibiting the function or differentiation of allergen-specific Th2 cells are discussed. It is shown that an IL-4R and IL-13R antagonist inhibits IL-4-driven Th2 cell differentiation and human IgE production both in vitro and in SCID-hu mice. In addition, it is discussed that allergen-specific Th2 cells can be rendered anergic following stimulation with allergen-derived peptides, representing T cell activation inducing epitopes. These anergic Th2 cells fail to produce IL-4, IL-5 and IL-13, to proliferate, and to provide help to B cells for IgE synthesis after rechallenge with allergen- and **antigen-presenting cells.** Finally, it is shown that IL-4-driven allergen-specific Th2 cell differentiation can be redirected into a Th0 and Th1 cell differentiation pathway by stimulating these IL-4-driven allergen-specific Th cell populations in the presence of IL-12, or by co-stimulating these cells via a novel T cell receptor, designated signalling lymphocyte activation molecule (SLAM). The clinical implications of these approaches are discussed.

L11 ANSWER 37 OF 39 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN

1995:355276 Document No.: PREV199598369576. The high affinity IgE receptor (FC-epsilon-RI) mediates IgE-dependent allergen presentation. Maurer, Dieter [Reprint author]; Ebner, Christof; Reininger, Baerbel; Fiebiger, Edda; Kraft, Dietrich; Kinet, Jean-Pierre; Stingl, Georg. Div. Immunol., Allergy Infectious Diseases, Dep. Dermatol., Univ. Vienna Med. Sch., Waehringer Guertel 18-20, A-1090 Vienna, Austria. Journal of Immunology, (1995) Vol. 154, No. 12, pp. 6285-6290.
CODEN: JOIMA3. ISSN: 0022-1767. Language: English.

AB The discovery that the high affinity IgE receptor (Fc-epsilon-RI) is expressed on APCs of patients with atopic diseases raised the possibility that the functional importance of Fc-epsilon-RI in the pathogenesis of atopy may extend beyond its role in type I allergic reactions. Here we show that, following removal of in vivo-bound IgE by lactic acid treatment, **targeting** of allergens to monocytes by Ag-specific IgE critically depends on Fc-epsilon-RI expression. Even more importantly, lactic acid-treated, monocyte-enriched PBMCs present allergen to T cells 100- to 1000-fold more effectively if the allergen has been targeted to Fc-epsilon-RI on these cells via allergen-specific IgE. This mechanism may critically lower the atopic individual's threshold to mount allergen-specific T cell responses capable of promoting IgE production and delayed-type hypersensitivity reactions.

L11 ANSWER 38 OF 39 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN

1995:299218 Document No.: PREV199598313518. Immunoglobulin E-binding structures on **antigen-presenting cells** present in skin and blood. Maurer, Dieter [Reprint author]; Stingl, Goerg. Div. Immunology, Allergy, Infectious Dsieases, Dep. Dermatol., Univ. Vienna Med. Sch., Waehringer Guertel 18-20, A-1090 Vienna, Austria. Journal of Investigative Dermatology, (1995) Vol. 104, No. 5, pp. 707-710.
CODEN: JIDEAE. ISSN: 0022-202X. Language: English.

AB In atopic individuals, cutaneous **antigen-presenting cells** (APC), i.e., Langerhans cells and dermal dendritic cells, frequently display anti-IgE reactivity. Although earlier observations suggested that this phenomenon results from the binding of complexed IgE to the low-affinity IgE receptor (Fc-epsilon-ERII/CD23), we and others demonstrated recently that Langerhans cells, dermal dendritic cells, and peripheral blood monocytes from atopic individuals can bind monomeric IgE via the high-affinity receptor for IgE (Fc-epsilon-RI). These new observations re-stimulated investigations aiming to unravel the nature and functionality of the relevant in vivo IgE-binding moiety(-ies) on APC. New data demonstrate that Fc-epsilon-RI, both quantitatively and qualitatively, is the pivotal serum IgE-binding structure on APC of atopics and, even more important, that Fc-epsilon-RI on APC functions as an allergen-focusing molecule. Thus, it is likely that allergens may be more efficiently taken up, processed, and presented to T cells after **targeting** to APC via Fc-epsilon-RI as compared with allergen binding to APC in the conventional manner. In vivo, Fc-epsilon-RI-IgE-dependent allergen presentation may critically lower atopic individuals' threshold to mount allergen-specific T-cell responses. This would result in the perpetuation of allergen-specific IgE production (type I reactions) and perhaps even the occurrence of T-cell-mediated, delayed-type hypersensitivity reactions in allergen-exposed tissues.

L11 ANSWER 39 OF 39 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN

1995:543163 Document No.: PREV199698557463. Regulation and **targeting** of T-cell immune responses by IgE and IgG antibodies. Escura, R. Bheekha; Wasserbauer, E.; Hammerschmid, F.; Pearcé, A.; Kidd, P.; Mudde, G. C. [Reprint author]. SANDOZ Res. Inst., Dep. Immuno-Dermatol., Allergy Section, Brunner Strasse 59, A-1235 Vienna, Austria. Immunology, (1995) Vol. 86, No. 3, pp. 343-350.
CODEN: IMMUAM. ISSN: 0019-2805. Language: English.

AB A set of chimeric antibodies with identical F(ab')-2 fragments specific for the hapten 5-iodo-4-hydroxyl-3-nitrophenacetyl (NIP), but with different human Fc parts (gamma-1, gamma-2, gamma-3, gamma-4, epsilon), was used to compare the role of IgG and IgE antibodies in antigen presentation by human Epstein-Barr virus (EBV) B cells. Two or three molecules of NIP were coupled to one molecule of Der pI (Der pI(3)NIP), a major allergen of Dermatophagoides pteronyssinus. Both monomeric IgG and preformed complexes of various Der pI/IgG ratios failed to hind significantly to the Fc receptor for IgG on B cells (Fc-gamma-RII; CD32). Binding of IgG3 (gt IgG1)-containing complexes (optimal ratio of antigen to antibody = 1:1) could be enhanced by increasing the number of haptens per Der pI molecule to nine or more. However, antigen presentation mediated by IgG and CD32 was not seen with either pulsed B cells or B cells that were allowed to capture the IgG complexes during the whole stimulation period. IgE binding to CD23 and subsequent IgE-mediated antigen presentation was seen under all conditions tested. Even monomeric immune complexes (IC) (DerpI-(3)NIP/IgE), in the absence of CD23 cross-linking, induced an immune response. As the number of natural epitopes for human antibodies on Der pI was less than five, we conclude that, in vivo, complexes consisting of DerpI/IgG will be directed to **antigen-presenting cells** expressing the high-affinity receptor for IgG (CD64), whereas IgE will allow antigen presentation by CD23-expressing cells, including B cells.

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L13 0 L2 AND ENCAPSULATED ALLERGEN

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L15 ANSWER 1 OF 2 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED.
on STN DUPLICATE 1
97201671 EMBASE Document No.: 1997201671. Functional CD86 (B7-2/B70) is predominantly expressed on Langerhans cells in atopic dermatitis. Ohki O.; Yokozeki H.; Katayama I.; Umeda T.; Azuma M.; Okumura K.; Nishioka K.. O. Ohki, Department of Dermatology, Tokyo Medical/Dental University, School of Medicine, 5-45, Yushima-1-chome, Bunkyo-ku, Tokyo, Japan. British Journal of Dermatology 136/6 (838-845) 1997.
Refs: 29.
ISSN: 0007-0963. CODEN: BJDEAZ. Pub. Country: United Kingdom. Language: English. Summary Language: English.
AB Recently, we reported the functional expression of CD86 on cultured human Langerhans cells derived from normal epidermis. In the present study, we investigated the expression and function of costimulatory molecules in the pathogenesis of atopic dermatitis. In immunohistochemical analysis. CD80 and/or CD86 were detected on dendritic-shaped cells not only in the epidermis but also in the dermis in the inflammatory lesions of atopic dermatitis (n = 12). CD80 was expressed in only five cases (42%), while CD86 was expressed in all cases (100%). These molecules were not detected in normal control subjects (n = 8). In non-lesional skin of atopic dermatitis (n = 4), CD86 but not CD80 was detected in one case. CD86 was preferentially induced on dendritic-shaped cells in positive patch test sites to Dermatophagoides pteronyssinus or house dust allergen in atopic dermatitis (n = 4). The CD80- or CD86-positive cells were confirmed as Langerhans cells by double immunostaining using anti-CD1a monoclonal

antibody. Neither CD86 nor CD80 was detected on keratinocytes. Similar results of the stronger expression of CD86 over that of CD80 were obtained from psoriasis vulgaris (n = 11) and from contact dermatitis (n = 7), although CD86 was expressed only in 57% of the contact dermatitis cases. The percentage of Langerhans cells positive for CD86 was higher than for CD80, i.e. 48% compared with 9%, respectively, in the epidermis of lesional skin of atopic dermatitis (n = 8). The expression rate of these molecules on Langerhans cells increased in the dermis. To investigate the function of co-stimulatory molecules on Langerhans cells in atopic dermatitis, we conducted an inhibition test with antibodies. Anti- CD86 monoclonal antibody almost completely inhibited T-cell proliferation stimulated with **crude extract** of D. pteronyssinus in the presence of epidermal cells as **antigen-presenting cells**, whereas anti-CD80 monoclonal antibody produced less of an inhibitory effect. These data indicate that CD86 expressed on Langerhans cells may play an important part in the pathogenesis of atopic dermatitis.

L15 ANSWER 2 OF 2 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

90218942 EMBASE Document No.: 1990218942. The use of human T-lymphocyte clones to study T-cell function in allergic contact dermatitis to urushiol. Kalish R.S.. Department of Dermatology, University of Minnesota, 420 Delaware Street S.E., Minneapolis, MN 55455-0392, United States. Journal of Investigative Dermatology 94/6 SUPPL. (108S-111S) 1990. ISSN: 0022-202X. CODEN: JIDEAE. Pub. Country: United States. Language: English. Summary Language: English.

AB Allergic contact dermatitis to poison ivy (Toxicodendron radicans) is believed to be mediated by T lymphocytes specific for the hapten urushiol. Activated T lymphocytes may produce pathology by a variety of mechanisms including direct cytotoxicity, production of lymphokines, recruitment of non-specific effector cells, non-specific cytotoxicity, and possibly autologous DR reactivity. The regulation and pathogenesis of this condition was studied by cloning and characterizing urushiol-specific T cells from the peripheral blood of patients with poison ivy dermatitis. Multiple CD8+ (T8+) urushiol-specific clones were derived. All clones the proliferated in response to a **crude extract** of T. radicans also proliferated in response to purified urushiol. Thus, urushiol appears to be the single immunogenic component of T. radicans resin. Pentadecylcatechol (PDC), which differs from urushiol only in the lack of unsaturated bonds in its lipophilic tail, stimulated only one of seven clones tested. This suggests that the double bonds in the C15 lipophilic tail of urushiol are required for antigenicity. Several of the CD8+ urushiol-specific clones suppressed pokeweed mitogen-induced IgG production in the presence of urushiol. Suppression was triggered specifically by urushiol and required MHC compatibility both for the **antigen-presenting cells** and the responding B cells. These suppressor clones were isolated from convalescent blood and may represent a mechanism for the termination of an allergic contact dermatitis.

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               )

=> s l16 and antigen presenting cell
L17          82 L16 AND ANTIGEN PRESENTING CELL

=> s l17 and modulating immune response
L18           0 L17 AND MODULATING IMMUNE RESPONSE

=> s l17 and allergy
L19           2 L17 AND ALLERGY

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PROCESSING COMPLETED FOR L19
L20 2 DUP REMOVE L19 (0 DUPLICATES REMOVED)

=> d l20 1-2 cbib abs

L20 ANSWER 1 OF 2 CAPLUS COPYRIGHT 2004 ACS on STN
2001:676622 Document No. 135:225857 Microbial delivery system. **Caplan, Michael** (Panacea Pharmaceuticals, LLC, USA). PCT Int. Appl. WO 2001066136 A2 20010913, 57 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US33121 20001206. PRIORITY: US 2000-PV195035 20000306.

AB The present invention provides methods and compns. for treating or preventing allergic responses, particularly anaphylactic allergic responses, in subjects who are allergic to allergens or susceptible to **allergies.** Methods of the present invention utilize administration of microorganisms to subjects, where the microorganisms produce allergens and protect the subjects from exposure to the allergens until phagocytosed by **antigen-presenting cells** . Particularly preferred microorganisms are gram-neg. bacteria, gram-pos. bacteria, and yeast. Particularly preferred allergens are proteins found in foods, venoms, drugs and latex that elicit allergic reactions and anaphylactic allergic reactions in individuals who are allergic to the proteins or are susceptible to **allergies** to the proteins. The proteins may also be modified to reduce the ability of the proteins to bind and crosslink IgE antibodies and thereby reduce the risk of eliciting anaphylaxis without affecting T-cell mediated Th1-type immunity.

L20 ANSWER 2 OF 2 CAPLUS COPYRIGHT 2004 ACS on STN
2000:741936 Document No. 133:308997 Methods for skewing the balance between Th1 and Th2 immune responses. **Bottomly, H. Kim; Caplan, Michael J.**; Sosin, Howard B. (Panacea Pharmaceuticals, LLC, USA). PCT Int. Appl. WO 2000061157 A1 20001019, 76 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US9270 20000407. PRIORITY: US 1999-290029 19990409.

AB The present invention provides compns. and methods for regulating immune system reactions by biasing T cell responses away from Th1 or Th2 responses in a pre-determined manner. Control is effected at the stage of antigen/APC encounter and/or at the stage of APC/T cell encounter. In preferred embodiments, a Th1 or Th2 response is inhibited through induction of the alternative response. The inventive methods and reagents are particularly useful for the management of autoimmune disorders, **allergy**, and asthma.

=> dup remove l17
PROCESSING COMPLETED FOR L17
L21 40 DUP REMOVE L17 (42 DUPLICATES REMOVED)

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L21 ANSWER 1 OF 40 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

2004210113 EMBASE CD4 Raft Association and Signaling Regulate Molecular Clustering at the Immunological Synapse Site. Balamuth F.; Brogdon J.L.; **Bottomly K.**. Dr. K. Bottomly, Section of Immunobiology, Yale University School of Medicine, 330 Cedar Street, New Haven, CT 06510, United States. Kim.Bottomly@yale.edu. Journal of Immunology 172/10 (5887-5892) 15 May 2004.
Refs: 29.
ISSN: 0022-1767. CODEN: JOIMA3. Pub. Country: United States. Language: English. Summary Language: English.

AB T cell activation is associated with the partitioning of TCRs and other signaling proteins, forming an immunological synapse. This study demonstrates a novel function for the CD4 coreceptor in regulating molecular clustering at the immunological synapse site. We show using transgenic mouse and retroviral reconstitution studies that CD4 is required for TCR/protein kinase C (PKC) θ clustering. Specifically, we demonstrate that CD4 palmitoylation sequences are required for TCR/PKCθ raft association and subsequent clustering, indicating a particular role for raft-associated CD4 molecules in regulating immune synapse organization. Although raft association of CD4 is necessary, it is not sufficient to mediate clustering, as cytoplasmic tail deletion mutants are able to localize to rafts, but are unable to mediate TCR/PKCθ clustering, indicating an additional requirement for CD4 signaling. These studies suggest that CD4 coreceptor function is regulated not only through its known signaling function, but also by posttranslational lipid modifications which regulate localization of CD4 in lipid rafts.

L21 ANSWER 2 OF 40 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

2004134494 EMBASE IL-4-Dependent Th2 Collateral Priming to Inhaled Antigens Independent of Toll-Like Receptor 4 and Myeloid Differentiation Factor 88. Eisenbarth S.C.; Zhadkevich A.; Ranney P.; Herrick C.A.; **Bottomly K.**. Dr. S.C. Eisenbarth, Department of Immunobiology, Yale University School of Medicine, 300 Cedar Street, New Haven, CT 06520, United States. stephanie.eisenbarth@yale.edu. Journal of Immunology 172/7 (4527-4534) 1 Apr 2004.
Refs: 50.
ISSN: 0022-1767. CODEN: JOIMA3. Pub. Country: United States. Language: English. Summary Language: English.

AB Allergic asthma is an inflammatory lung disease thought to be initiated and directed by type 2 helper T cells responding to environmental Ags. The mechanisms by which allergens induce Th2-adaptive immune responses are not well understood, although it is now clear that innate immune signals are required to promote DC activation and Th2 sensitization to inhaled proteins. However, the effect of ongoing Th2 inflammation, as seen in chronic asthma, on naive lymphocyte activation has not been explored. It has been noted that patients with atopic disorders demonstrate an increased risk of developing sensitivities to new allergens. This suggests that signals from an adaptive immune response may facilitate sensitization to new Ags. We used a Th2-adoptive transfer murine model of asthma to identify a novel mechanism, termed "collateral priming," in which naive CD4(+) T cells are activated by adaptive rather than innate immune signals. Th2 priming to newly encountered Ags was dependent on the production of IL-4 by the transferred Th2 population but was independent of Toll-like receptor 4 signaling and the myeloid differentiation factor 88 Toll-like receptor signaling pathway. These results identify a novel mechanism of T cell priming in which an Ag-specific adaptive immune response initiates distinct Ag-specific T cell responses in the absence of classical innate immune system triggering signals.

L21 ANSWER 3 OF 40 CAPLUS COPYRIGHT 2004 ACS on STN

2003:76646 Document No. 138:121628 Tumor-associated antigen or tumor cell components haptenized with urushiols for treating cancer. **Caplan, Michael J.; Bottomly, Kim H.** (Panacea Pharmaceuticals, LLC, USA; Seer Pharmaceuticals, LLC). PCT Int. Appl. WO 2003007987 A2 20030130, 44 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA,

BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2002-US22877 20020718. PRIORITY: US 2001-PV306228 20010718; US 2002-197376 20020717.

AB The present invention provides techniques and reagents that induce an immune response against tumor cells. According to the invention, tumor cell components are contacted with a sensitizing agent, preferably so that one or more tumor cell components become haptenized with a sensitizing agent, and the resulting combination is administered to a patient suffering from a tumor, so that an anti-tumor immune response is mounted. The haptenizing or sensitizing agent is compound naturally produced by poison ivy, poison oak, or poison sumac plants e.g. a urushiol. In some embodiments of the invention, sensitizing agent/tumor cell component compns. are administered directly to a patient; in other embodiments they are administered by means of an **antigen presenting cell** such as a dendritic cell.

L21 ANSWER 4 OF 40 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

2003476054 EMBASE The master regulators of allergic inflammation: Dendritic cells in Th2 sensitization. Eisenbarth S.C.; Piggott D.A.; **Bottomly K.**. S.C. Eisenbarth, Yale University, Department of Immunobiology, 300 Cedar Street, New Haven, CT 06510, United States. kim.bottomly@yale.edu. Current Opinion in Immunology 15/6 (620-626) 2003.
Refs: 55.
ISSN: 0952-7915. CODEN: COPIEL. Pub. Country: United Kingdom. Language: English. Summary Language: English.

AB The development of Th2 responses to inhaled proteins represents a malfunction of the adaptive immune system in that protein antigens are not microbial in nature and should not elicit an adaptive immune reaction. This derailing of the immune system may result from false alarms generated by the innate immune system, resulting in unexpected dendritic cell (DC) maturation after exposure to allergens. Conditions in the local microenvironment during DC maturation may also result in the preferential induction of Th2 responses. Recent progress has been made in our understanding of the role of DCs in both Th2 sensitization to aeroallergens and the regulation of Th2 and Th1 immunity.

L21 ANSWER 5 OF 40 MEDLINE on STN DUPLICATE 1

2002678463. PubMed ID: 12438442. Resident lung **antigen-presenting cells** have the capacity to promote Th2 T cell differentiation in situ. Constant Stephanie L; Brogdon Jennifer L; Piggott Damani A; Herrick Christina A; Visintin Irene; Ruddle Nancy H; **Bottomly Kim.** (Section of Immunobiology, Yale University School of Medicine, New Haven, Connecticut, USA.. mtmslc@gwumc.edu) . Journal of clinical investigation, (2002 Nov) 110 (10) 1441-8. Journal code: 7802877. ISSN: 0021-9738. Pub. country: United States. Language: English.

AB Antigen exposure via airway epithelia is often associated with a failure to prime or with the preferential priming of Th2 cells. We previously reported that the intranasal delivery of a Th1-inducing antigen promoted Th2-dominated responses, rather than the expected Th1 responses. Thus, we proposed that when pulmonary T cell priming is induced, the lung microenvironment might intrinsically favor the generation of Th2 types of responses. To establish a potential mechanism for such preferential priming, we examined the initial interactions between antigens and resident **antigen-presenting cells** (APCs) within the lung. We show that intranasally delivered antigens are preferentially taken up and can be presented to antigen-specific T cells by a resident population of CD11c(bright) APCs. Most of these

antigen-loaded APCs remained within lung tissues, and migration into secondary lymphoid organs was not crucial for T cell priming to occur within the pulmonary tract. Furthermore, these pulmonary APCs demonstrated a marked expression of IL-6 and IL-10 within hours of antigen uptake, suggesting that resident tissue APCs have the capacity to promote Th2 T cell differentiation in situ.

L21 ANSWER 6 OF 40 CAPLUS COPYRIGHT 2004 ACS on STN
2001:676622 Document No. 135:225857 Microbial delivery system. **Caplan, Michael** (Panacea Pharmaceuticals, LLC, USA). PCT Int. Appl. WO 2001066136 A2 20010913, 57 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US33121 20001206. PRIORITY: US 2000-PV195035 20000306.

AB The present invention provides methods and compns. for treating or preventing allergic responses, particularly anaphylactic allergic responses, in subjects who are allergic to allergens or susceptible to allergies. Methods of the present invention utilize administration of microorganisms to subjects, where the microorganisms produce allergens and protect the subjects from exposure to the allergens until phagocytosed by **antigen-presenting cells.** Particularly preferred microorganisms are gram-neg. bacteria, gram-pos. bacteria, and yeast. Particularly preferred allergens are proteins found in foods, venoms, drugs and latex that elicit allergic reactions and anaphylactic allergic reactions in individuals who are allergic to the proteins or are susceptible to allergies to the proteins. The proteins may also be modified to reduce the ability of the proteins to bind and crosslink IgE antibodies and thereby reduce the risk of eliciting anaphylaxis without affecting T-cell mediated Th1-type immunity.

L21 ANSWER 7 OF 40 CAPLUS COPYRIGHT 2004 ACS on STN
2001:416792 Document No. 135:10056 Controlled delivery of antigens. **Caplan, Michael**; Burks, Wesley A., Jr.; Bannon, Gary A. (The Board of Trustees of the University of Arkansas, USA; Panacea Pharmaceuticals, LLC). PCT Int. Appl. WO 2001039800 A2 20010607, 34 pp. DESIGNATED STATES: W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG, TR. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US42607 20001206. PRIORITY: US 1999-PV169330 19991206.

AB Formulations and methods are developed for delivering antigens to individuals in a manner that substantially reduces contact between the antigen and IgE receptors displayed on the surfaces of cells involved in mediating allergic responses, which target delivery of antigen to dendritic, phagocytic and **antigen presenting cells** (APCs), and which have improved pharmacokinetics. By reducing direct and indirect association of antigens with antigen-specific IgE antibodies, the risk of an allergic reaction, possibly anaphylactic shock, is reduced or eliminated. Particularly preferred antigens are those that may elicit anaphylaxis in individuals, including food antigens, insect venom and rubber-related antigens. In the preferred embodiments, the compns. include one or more antigens in a delivery material such as a polymer, in the form of particles or a gel, or lipid vesicles or liposomes, any of which can be stabilized or targeted to enhance delivery. Preferably, the antigen is surrounded by the encapsulation material.

Alternatively or addnl., the antigen is displayed on the surface of the encapsulation material. One result of encapsulating antigen is the reduction in association with antigen-specific IgE antibodies. In some embodiments, antigens are stabilized or protected from degradation until the antigen can be recognized and endocytized by APCs which are involved in eliciting cellular and humoral immune responses. In a preferred embodiment, the formulation is designed to deliver antigens to individuals in a manner designed to promote a Th1-type mediated immune response and/or in a manner designed to suppress a Th2 response. In still another embodiment, the formulation effects preferential release of the antigen within APCs. For example, various synthetic, biodegradable polymeric microsphere formulations were prepared containing peanut allergen. Microspheres based on poly(lactide-co-glycolide) (75:25) containing an acid end group (0.1% loaded with allergen) had the lowest amount (<20 ng) of peanut protein detected on the outside of the microsphere and the best range of peanut protein allergens contained within the microspheres (having mol. wts. ranging from 15 kDa to 70 kDa).

L21 ANSWER 8 OF 40 CAPLUS COPYRIGHT 2004 ACS on STN
2000:741936 Document No. 133:308997 Methods for skewing the balance between Th1 and Th2 immune responses. **Bottomly, H. Kim; Caplan, Michael J.**; Sosin, Howard B. (Panacea Pharmaceuticals, LLC, USA). PCT Int. Appl. WO 2000061157 A1 20001019, 76 pp. DESIGNATED STATES: W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM; RW: AT, BE, BF, BJ, CF, CG, CH, CI, CM, CY, DE, DK, ES, FI, FR, GA, GB, GR, IE, IT, LU, MC, ML, MR, NE, NL, PT, SE, SN, TD, TG. (English). CODEN: PIXXD2. APPLICATION: WO 2000-US9270 20000407. PRIORITY: US 1999-290029 19990409.

AB The present invention provides compns. and methods for regulating immune system reactions by biasing T cell responses away from Th1 or Th2 responses in a pre-determined manner. Control is effected at the stage of antigen/APC encounter and/or at the stage of APC/T cell encounter. In preferred embodiments, a Th1 or Th2 response is inhibited through induction of the alternative response. The inventive methods and reagents are particularly useful for the management of autoimmune disorders, allergy, and asthma.

L21 ANSWER 9 OF 40 MEDLINE on STN DUPLICATE 2
1999371716. PubMed ID: 10441214. Regulation of naive T cell differentiation by varying the potency of TCR signal transduction. Leitenberg D; **Bottomly K.** (Section of Immunobiology and the Department of Laboratory Medicine, Yale University School of Medicine, New Haven, CT 06520-8011, USA.) Seminars in immunology, (1999 Aug) 11 (4) 283-92. Ref: 51. Journal code: 9009458. ISSN: 1044-5323. Pub. country: United States. Language: English.

AB The regulation of naive T cell development into different effector cell subsets is mediated by a complex interplay between the cytokine microenvironment, receptor ligand interactions on the T cell and the **antigen presenting cell**, and the potency of T cell receptor (TCR) signaling. In this review we will focus on how alterations in the strength of TCR ligation initiate different signal transduction patterns which regulate the developmental fate of naive T cells. We propose a model in which specific signals are required to initiate Th2 differentiation, but that this pathway can be inhibited following a strong TCR stimulus.

L21 ANSWER 10 OF 40 MEDLINE on STN
1999097083. PubMed ID: 9880255. STAT5 interaction with the T cell receptor complex and stimulation of T cell proliferation. Welte T; Leitenberg D; Dittel B N; al-Ramadi B K; Xie B; Chin Y E; Janeway C A Jr; Bothwell A L; **Bottomly K**; Fu X Y. (Department of Pathology, Yale University

School of Medicine, New Haven, CT 06520, USA.) Science, (1999 Jan 8) 283 (5399) 222-5. Journal code: 0404511. ISSN: 0036-8075. Pub. country: United States. Language: English.

AB The role of STAT (signal transducer and activator of transcription) proteins in T cell receptor (TCR) signaling was analyzed. STAT5 became immediately and transiently phosphorylated on tyrosine 694 in response to TCR stimulation. Expression of the protein tyrosine kinase Lck, a key signaling protein in the TCR complex, activated DNA binding of transfected STAT5A and STAT5B to specific STAT inducible elements. The role of Lck in STAT5 activation was confirmed in a Lck-deficient T cell line in which the activation of STAT5 by TCR stimulation was abolished. Expression of Lck induced specific interaction of STAT5 with the subunits of the TCR, indicating that STAT5 may be directly involved in TCR signaling. Stimulation of T cell clones and primary T cell lines also induced the association of STAT5 with the TCR complex. Inhibition of STAT5 function by expression of a dominant negative mutant STAT5 reduced antigen-stimulated proliferation of T cells. Thus, TCR stimulation appears to directly activate STAT5, which may participate in the regulation of gene transcription and T cell proliferation during immunological responses.

L21 ANSWER 11 OF 40 MEDLINE on STN DUPLICATE 3

1999420911. PubMed ID: 10493168. Function and regulation of memory CD4 T cells. Metz D P; **Bottomly K.** (Yale Medical School, Section of Immunobiology, New Haven, CT 06520, USA.) Immunologic research, (1999) 19 (2-3) 127-41. Ref: 78. Journal code: 8611087. ISSN: 0257-277X. Pub. country: United States. Language: English.

AB The development of peripheral naive CD4 T cells is dependent on the success of positive selection of immature T cells in the thymus. Only thymocytes that express a T cell receptor (TCR) capable of recognizing self-MHC with low affinity are selected for survival and differentiation into mature naive T cells. Although the TCR of naive T cells has to maintain self-tolerance, it also propagates naive CD4 T cell proliferation on recognition of appropriate foreign peptide associated with MHC class II on **antigen-presenting cells** (APCs). Naive CD4 T cells that successfully engage foreign peptide undergo further differentiation that leads to the maturation of a select few into the memory T cell pool. Although the requirements that lead to memory T cell development are currently not known, functional changes have been described that are thought to be associated with the greater efficiency with which memory T cells respond to antigen. This article will discuss differences associated with signaling through the TCR of naive and memory CD4 T cells and describe unique control mechanisms imposed on memory CD4 T cells that are likely to have ari sen to counterbalance the altered TCR signaling.

L21 ANSWER 12 OF 40 MEDLINE on STN

1999049810. PubMed ID: 9834064. Differential role of CTLA-4 in regulation of resting memory versus naive CD4 T cell activation. Metz D P; Farber D L; Taylor T; **Bottomly K.** (Immunobiology Section, Yale University School of Medicine, New Haven, CT 06510, USA.) Journal of immunology (Baltimore, Md. : 1950), (1998 Dec 1) 161 (11) 5855-61. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB Regulation of peripheral T cell responses is critical for preserving self tolerance. Memory T cells have a lower threshold for activation through the TCR and are thought to be less dependent on costimulation than naive T cells, suggesting a requirement for more stringent regulation of memory T cells. We have recently shown that CD4 engagement apart from the TCR results in the inactivation of memory, but not naive, CD4 T cells. We show here that this inhibition requires ligation of CTLA-4, in that blocking CTLA-4-B7 interactions restores memory CD4 T cell responsiveness. Early signaling through CTLA-4 is possible because resting memory, but not naive, CD4 T cells contain intracellular stores of CTLA-4 that are continuously recycled between the cytoplasm and the cell surface. This mechanism ensures that low intensity TCR engagements, which are thought to

be important for peripheral T cell longevity, do not cause memory T cell activation but instead raise their threshold for costimulatory signals. This may give memory T cells an extended lifespan with a reduced risk of inappropriate activation.

L21 ANSWER 13 OF 40 MEDLINE on STN
97272140. PubMed ID: 9126985. Induction of IL-4-producing CD4+ T cells by antigenic peptides altered for TCR binding. Tao X; Grant C; Constant S; **Bottomly K.** (Section of Immunobiology, Yale University School of Medicine and Howard Hughes Medical Institute, New Haven, CT 06520, USA.) Journal of immunology (Baltimore, Md. : 1950), (1997 May 1) 158 (9) 4237-44. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB The adaptive immune responses to foreign Ags are primarily regulated by the cytokines produced by CD4 T cells. The generation of distinct cytokine-producing T cell subsets has been shown to be influenced by a number of factors, including cytokines, different types of APCs, and the amounts of priming Ag. We have previously reported that the affinity of an antigenic peptide for its presenting MHC class II molecules and that different doses of Ag peptide affect the outcome of the functional CD4 T cell response. In the current study, we further examined the impact of the affinity of an antigenic peptide for its TCR on CD4 T cell priming. We generated a panel of Ag peptide variants mutated at positions known to be critical for binding to a well-characterized TCR (known as altered peptide ligands, or APLs). Compared with the WT peptide, these APLs are defective in stimulating the proliferative responses of T cells. However, they can effectively prime in vitro naive CD4 T cells for differentiation into both Th1-like and Th2-like cells. In contrast, the WT peptide primes only for IFN-gamma-producing Th1-like cells. Using highly purified dendritic cells as APCs to present the APL or WT peptide leads to the same pattern of priming as using total splenic APCs. These results indicate that priming by APLs for both IL-4 production and IFN-gamma production does not require two different types of APCs. In summary, our data indicate that APL can directly stimulate naive CD4 T cells to become Th2 effector cells.

L21 ANSWER 14 OF 40 SCISEARCH COPYRIGHT (c) 2004 The Thomson Corporation. on STN
97:307400 The Genuine Article (R) Number: WT669. Induction of TH1 and TH2 CD4+ T cell responses: The alternative approaches. Constant S L (Reprint); **Bottomly K.** YALE UNIV, SCH MED, IMMUNOBIOL SECT, 333 CEDAR ST, NEW HAVEN, CT 06510 (Reprint); YALE UNIV, SCH MED, HOWARD HUGHES MED INST, NEW HAVEN, CT 06510. ANNUAL REVIEW OF IMMUNOLOGY (DEC 1997) Vol. 15, pp. 297-322. Publisher: ANNUAL REVIEWS INC. 4139 EL CAMINO WAY, PO BOX 10139, PALO ALTO, CA 94303-0139. ISSN: 0732-0582. Pub. country: USA. Language: English.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB T helper lymphocytes can be divided into two distinct subsets of effector cells based on their functional capabilities and the profile of cytokines they produce. The Th1 subset of CD4(+) T cells secretes cytokines usually associated viith inflammation, such as IFN-gamma and TNF and induces cell-mediated immune responses. The Th2 subset produces cytokines such as IL-4 and IL-5 that help B cells to proliferate and differentiate and is associated with humoral-type immune responses. The selective differentiation of either subset is established during priming and can be significantly influenced by a variety of factors. One of these factors, the cytokine environment, has been put forward as the major variable influencing Tn development and is already well reviewed by others. Instead, in the current review, we focus on some of the alternative approaches for skewing Th1/Th2 responses. Specifically, we discuss the effects on Th priming of (a) using altered peptide ligands as antigens, (b) varying the dose of antigen, and (c) altering costimulatory signals. The potential importance of each of these variables to influence immune responses to pathogens in vivo is discussed throughout.

L21 ANSWER 15 OF 40 MEDLINE on STN DUPLICATE 4
96136767. PubMed ID: 8551228. The extracellular domain of CD45 controls association with the CD4-T cell receptor complex and the response to antigen-specific stimulation. Leitenberg D; Novak T J; Farber D; Smith B R; **Bottomly K.** (Howard Hughes Medical Institute, Section of Immunobiology, Yale University School of Medicine, New Haven, Connecticut 06510, USA.) Journal of experimental medicine, (1996 Jan 1) 183 (1) 249-59. Journal code: 2985109R. ISSN: 0022-1007. Pub. country: United States. Language: English.

AB The CD45 tyrosine phosphatase plays an important role in regulating T lymphocyte activation, but the function of the different isoforms of CD45 is not known. T cell transfectants have been prepared that express individual CD45 isoforms in cells with a well-defined T cell receptor (TCR) from the D10 T helper 2 clone. We find that cells bearing low molecular weight CD45 isoforms are far more efficient in responding to stimulation with peptide and **antigen-presenting cells** compared with cells bearing high molecular weight CD45 isoforms. One hypothesis for the preferential activation of cells that express low molecular weight CD45 isoforms is that they interact with other cell surface antigens important in TCR signaling, altering their phosphorylation status and affecting the character of the signal transduction pathway. In this report, using cells expressing single isoforms, we demonstrate that low molecular weight isoforms of CD45 preferentially associate with CD4 and the TCR complex compared with high molecular weight isoforms. The molecular basis for this interaction was further examined using a glycosyl phosphatidyl inositol (GPI)-linked form of CD45Null (lacking tyrosine phosphatase domains), which preferentially associated with CD4 compared with GPI-linked CD45ABC, and cytoplasmic tail mutants of CD4, which retained the ability to coassociate. Using this panel of transfectants, it is clear that the interaction between CD4 and CD45 does not require the cytoplasmic domains of CD45, but is dependent on the specific external domain of the various isoforms: low molecular weight species were more likely to associate with the CD4-TCR complex than the higher molecular weight isoforms, and their ability to coassociate correlated with the magnitude of the response to specific antigen.

L21 ANSWER 16 OF 40 MEDLINE on STN DUPLICATE 5
95248056. PubMed ID: 7730604. Peptide and protein antigens require distinct **antigen-presenting cell** subsets for the priming of CD4+ T cells. Constant S; Sant'Angelo D; Pasqualini T; Taylor T; Levin D; Flavell R; **Bottomly K.** (Section of Immunobiology, Yale University School of Medicine, New Haven, CT 06510, USA.) Journal of immunology (Baltimore, Md. : 1950), (1995 May 15) 154 (10) 4915-23. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB Priming of naive CD4+ T cells to Ag requires an **antigen-presenting cell** (APC) that can take up the Ag and present peptide bound to MHC class II molecules. We have used both in vivo and in vitro approaches to demonstrate that the APC used to prime naive CD4+ T cells depends on the initial form in which an Ag is administered. Although Ag delivered as a peptide was presented most efficiently to CD4+ T cells by DC, these APC were poor at priming to a protein form of the same Ag. In contrast, the presence of B cells was a requisite for priming to protein Ag.

L21 ANSWER 17 OF 40 MEDLINE on STN DUPLICATE 6
96003410. PubMed ID: 7561077. B lymphocytes can be competent **antigen-presenting cells** for priming CD4+ T cells to protein antigens in vivo. Constant S; Schweitzer N; West J; Ranney P; **Bottomly K.** (Section of Immunobiology, Yale University School of Medicine, New Haven, CT 06510, USA.) Journal of immunology (Baltimore, Md. : 1950), (1995 Oct 15) 155 (8) 3734-41. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB The potential role of different subsets of APCs to stimulate naive CD4+ T cells to peptide and protein Ags in vivo was examined. Mice lacking B

cells (microMT knockout mice) were impaired in their priming to protein but not peptide Ags, suggesting a requirement for B cells in priming to protein Ags in vivo. Experiments designed to determine the ability of splenic dendritic cells (DCs) and B lymphocytes to take up peptide or protein Ags in vivo demonstrated that peptide Ags were taken up preferentially by DCs, whereas proteins were taken up by Ag-specific B cells in vivo. A further examination of the Ag-specific B cells pulsed in vivo with protein Ags revealed a marked up-regulation in surface expression of B7-2 costimulatory molecules, detectable as early as 4 h after Ag administration. Based on their potency in the uptake and processing of protein Ags as well as their ability to up-regulate costimulatory molecules through Ag internalization, we suggest that Ag-specific B cells will be an important APC in priming naive CD4+ T cells to protein Ags in vivo.

L21 ANSWER 18 OF 40 MEDLINE on STN DUPLICATE 7

96011850. PubMed ID: 7589109. CD4 and CD45 regulate qualitatively distinct patterns of calcium mobilization in individual CD4+ T cells. Leitenberg D; Constant S; Lu D D; Smith B R; **Bottomly K.** (Howard Hughes Medical Institute, Section of Immunobiology, Yale University School of Medicine, New Haven, CT 06520-8011, USA.) European journal of immunology, (1995 Sep) 25 (9) 2445-51. Journal code: 1273201. ISSN: 0014-2980. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.

AB An early consequence of T cell activation is an increase in intracellular calcium concentration. Recent advances in video laser microscopic techniques enable the examination of individual cells over time following stimulation. Such studies have revealed that cells can undergo qualitatively distinct patterns of calcium mobilization, suggesting that different patterns of calcium flux may be associated with different signaling pathways and may differentially affect late events in cell activation. In this report, we identify distinct patterns of calcium mobilization in CD4+ T cells following the antibody-mediated cross-linking of either CD3 or CD4, or following the cross-linking of both CD3 and CD4 simultaneously. These effects can be further modified by the cross-linking of CD45. We find that antibody cross-linking of CD3 alone induces a single spike in the vast majority of cells shortly after the addition of the cross-linking antibody. In contrast, cross-linking CD4 alone induces a delayed pattern of repetitive calcium spikes which are decreased in amplitude compared to CD3 cross-linking. Simultaneous cross-linking of CD3 and CD4 induces a sustained increase in intracellular calcium mobilization which is dependent on the presence of extracellular calcium. This sustained increase in intracellular calcium concentration is also seen following physiologic cross-linking of CD3 and CD4 after T cell interaction with specific antigen and **antigen-presenting cells.** Finally, the simultaneous cross-linking of CD45, CD3 and CD4 abrogates the sustained increase in calcium seen following CD3 and CD4 cross-linking. These results suggest that the qualitative nature of T cell receptor signaling can be modulated by the molecular association of other signaling molecules, which may be part of the T cell receptor complex or not.

L21 ANSWER 19 OF 40 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

95330654 EMBASE Document No.: 1995330654. Extent of T cell receptor ligation can determine the functional differentiation of naive CD4+ T cells. Constant S.; Pfeiffer C.; Woodard A.; Pasqualini T.; **Bottomly K.** . Section of Immunobiology, Howard Hughes Medical Institute, Yale University School of Medicine, 310 Cedar Street,New Haven, CT 06510, United States. Journal of Experimental Medicine 182/5 (1591-1596) 1995. ISSN: 0022-1007. CODEN: JEMEAV. Pub. Country: United States. Language: English. Summary Language: English.

AB Naive CD4+ T cells can differentiate into cells predominantly involved in humoral immunity, known as T helper type 2 cells (Th2), or cells involved in cell-mediated immunity, known as Th1 cells. In this report, we show that priming of CD4+ T cells bearing a transgene-encoded T cell receptor

can lead to differentiation into Th1-like cells producing abundant interferon γ when the cells are exposed to high antigen doses, while low doses of the same peptide induce cells with the same T cell receptor to differentiate into Th2- like cells producing abundant interleukin 4. Thus antigen dose is one factor that can control the differentiation fate of a naive CD4+ T cell.

L21 ANSWER 20 OF 40 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN

1995:382525 Document No.: PREV199598396825. Induction of IL-4-producing CD4+ T cells by antigenic peptides altered for T cell receptor binding. Tao, X.; **Bottomly, K.**. Sect. Immunobiol., Yale Univ., Sch. Med., 310 Cedar St., New Haven, CT 06510, USA. 9TH INTERNATIONAL CONGRESS OF IMMUNOLOGY. (1995) pp. 324. The 9th International Congress of Immunology. Publisher: 9th International Congress of Immunology, San Francisco, California, USA. Meeting Info.: Meeting Sponsored by the American Association of Immunologists and the International Union of Immunological Societies. San Francisco, California, USA. July 23-29, 1995.
Language: English.

L21 ANSWER 21 OF 40 MEDLINE on STN DUPLICATE 8

95211652. PubMed ID: 7535181. Control of memory CD4 T cell activation: MHC class II molecules on APCs and CD4 ligation inhibit memory but not naive CD4 T cells. Farber D L; Luqman M; Acuto O; **Bottomly K.** (Section of Immunobiology, Howard Hughes Medical Institute, Yale University School of Medicine, New Haven, Connecticut 06510.) Immunity, (1995 Mar) 2 (3) 249-59. Journal code: 9432918. ISSN: 1074-7613. Pub. country: United States. Language: English.

AB Memory or antigen-experienced CD4 T cells differ from naive CD4 T cells both phenotypically by cell surface marker expression, and functionally by their dissimilar pattern of cytokine secretion and activation requirements through their T cell receptor (TCR). We show here that activation of memory CD4 T cells (CD45RBlo subset), but not naive CD4 T cells (CD45RBhi subset), is inhibited by MHC class II molecules on **antigen-presenting cells** and by CD4 ligation. We propose that the selective negative signal in memory cells is a direct result of the differences in signaling via CD4 and CD3, exemplified in the disparate pattern of tyrosine-phosphorylated proteins visible after activation of the two subsets. In vivo, this inhibitory signal may serve to prevent irrelevant interactions between memory CD4 T cells and bystander MHC class II+ cells, and may also be responsible for the defective functioning of memory CD4 T cells in AIDS.

L21 ANSWER 22 OF 40 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN

1995:326105 Document No.: PREV199598340405. Peptide and protein antigens require different **antigen presenting cell** types for the priming of CD4+ T cells. Constant, Stephanie; Pasqualini, Theresa; Taylor, Thomas; Levin, Ditza; Flavell, Richard; **Bottomly, Kim.** Immunobiol. Dep., Yale Univ. Sch. Med., New Haven, CT 06510, USA. Journal of Cellular Biochemistry Supplement, (1995) Vol. 0, No. 21A, pp. 91.
Meeting Info.: Keystone Symposium on Control and Manipulation of the Immune Response. Taos, New Mexico, USA. March 16-22, 1995.
ISSN: 0733-1959. Language: English.

L21 ANSWER 23 OF 40 SCISEARCH COPYRIGHT (c) 2004 The Thomson Corporation. on STN

95:651023 The Genuine Article (R) Number: QT864. PEPTIDE AND PROTEIN ANTIGENS REQUIRE DIFFERENT **ANTIGEN-PRESENTING CELL** -TYPES FOR THE PRIMING OF CD4+ T-CELLS. CONSTANT S (Reprint); PASQUALINI T; TAYLOR T; LEVIN D; FLAVELL R; **BOTTOMLY K.** YALE UNIV, SCH MED, DEPT IMMUNOBIOL, NEW HAVEN, CT, 06510. JOURNAL OF CELLULAR BIOCHEMISTRY (10 MAR 1995) Supp. 21A, pp. 91. ISSN: 0730-2312. Pub. country: USA. Language: ENGLISH.

L21 ANSWER 24 OF 40 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN

1995:380943 Document No.: PREV199598395243. B lymphocytes are the major APC for priming CD4+ T cells to protein antigens in vivo. Constant, S. L.; West, J.; **Bottomly, K.**. Yale Univ. Sch. Med., New Havne, CT, USA. 9TH INTERNATIONAL CONGRESS OF IMMUNOLOGY. (1995) pp. 56. The 9th International Congress of Immunology. Publisher: 9th International Congress of Immunology, San Francisco, California, USA.
Meeting Info.: Meeting Sponsored by the American Association of Immunologists and the International Union of Immunological Societies. San Francisco, California, USA. July 23-29, 1995.
Language: English.

L21 ANSWER 25 OF 40 SCISEARCH COPYRIGHT (c) 2004 The Thomson Corporation. on STN

94:685185 The Genuine Article (R) Number: PN127. BOTH HIGH AND LOW AVIDITY ANTIBODIES TO THE T-CELL RECEPTOR CAN HAVE AGONIST OR ANTAGONIST ACTIVITY. YOON S T (Reprint); DIANZANI U; **BOTTOMLY K**; JANEWAY C A. UNIV CALIF SAN FRANCISCO, DEPT ORTHOPED SURG, SAN FRANCISCO, CA, 94141 (Reprint); YALE UNIV, SCH MED, HOWARD HUGHES MED INST, IMMUNOBIOL SECT, NEW HAVEN, CT, 06510. IMMUNITY (OCT 1994) Vol. 1, No. 7, pp. 563-569. ISSN: 1074-7613. Pub. country: USA. Language: ENGLISH.
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Anti-TCR antibodies can activate or block the activation of T cells. In the present experiments, we have shown that different monoclonal antibodies to the same TCR can have either agonist or antagonist activity, and we have examined the relationship between these functional effects and the avidity of the antibody for the TCR. We show here that it is not the avidity of an anti-TCR antibody that determines whether it acts as an agonist or an antagonist. Moreover, we show that monovalent Fab fragments of agonist antibodies produce detectable changes in T cell behavior. These data suggest that T cell activation may involve not just aggregation of the TCR but also some induced change in individual ligated receptors, and that agonists may produce this change while antagonists do not. We argue that similar effects may apply to peptide-MHC ligands as well.

L21 ANSWER 26 OF 40 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN

1994:326529 Document No.: PREV199497339529. Memory CD4+ T cell activation is inhibited by MHC-class II-mediated CD4 crosslinking in the absence of co-stimulatory activity. Farber, Donna L. [Reprint author]; Luqman, Mohammed; **Bottomly, Kim.** Sect. Immunobiol., Yale Univ. Sch. Med., New Haven, CT 06510, USA. Journal of Cellular Biochemistry Supplement, (1994) Vol. 0, No. 18D, pp. 415.
Meeting Info.: Keystone Symposium on Lymphocyte Activation. Keystone, Colorado, USA. April 10-17, 1994.
ISSN: 0733-1959. Language: English.

L21 ANSWER 27 OF 40 MEDLINE on STN DUPLICATE 9

94123335. PubMed ID: 7904901. Signals and signs for lymphocyte responses. Janeway C A Jr; **Bottomly K.** (Section of Immunobiology, Yale University School of Medicine, New Haven, Connecticut 06510.) Cell, (1994 Jan 28) 76 (2) 275-85. Ref: 88. Journal code: 0413066. ISSN: 0092-8674. Pub. country: United States. Language: English.

AB The adaptive immune response protects us from infection in a world of pathogens that is forever evolving new variants. As the system is built on the generation of an open repertoire of receptors, the recognition of self is unavoidable, and is guarded against by deletion during lymphocyte development of those cells that are specific for ubiquitous self antigens, and the silencing of those that are specific for self antigens only encountered after cells achieve functional maturity in the periphery. This silencing occurs when lymphocytes recognize antigens in the absence of suitable costimulatory molecules. By contrast, when the same cell encounters the same ligand on a cell that expresses costimulatory

molecules, it will proliferate and differentiate into an effector cell. These effector cells mediate protective immunity when the antigen is carried by a pathogen, but they can mount autoimmune responses if the antigen is derived from self. The major costimulatory molecules for CD4 T cells appear to be B7 and B7.2 that bind to the CD28 and CTLA-4 receptors on the T cell. The signals from the TCR appear to be integrated with those from the costimulator receptor, and the T cell response depends on the precise nature of these signals, further conditioned by cytokines present in the environment of the responding cell. B cells can be viewed in a similar way, with the costimulatory molecule CD40 ligand and cytokines coming mainly from CD4 helper T cells determining the fate of the responding B cell. The TCR is not simply an on and off switch, since the precise way in which the TCR is ligated determines the differentiation of the T cell and can alter the effector responses of established T cell lines. Thus, the response capabilities of T cells are more flexible than originally believed, and much of this flexibility comes from the interplay of TCR signals and signs from the environment. If the biochemical nature of these differential signaling pathways were known, it might be possible to develop simple pharmacological agents capable of diverting T cell responses from harmful to innocuous by getting the T cell to reinterpret the signals it is receiving via its receptors.(ABSTRACT TRUNCATED AT 400 WORDS)

L21 ANSWER 28 OF 40 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN DUPLICATE 10

94004548 EMBASE Document No.: 1994004548. Role of dendritic cells in the priming of CD4+ T lymphocytes to peptide antigen in vivo. Levin D.; Constant S.; Pasqualini T.; Flavell R.; **Bottomly K.**. Section of Immunobiology, Yale University School of Medicine, 310 Cedar Street,New Haven, CT 06510, United States. Journal of Immunology 151/12 (6742-6750) 1993.
ISSN: 0022-1767. CODEN: JOIMA3. Pub. Country: United States. Language: English. Summary Language: English.

AB The contribution of dendritic cells (DC) in the initial priming of CD4+ T lymphocytes in vivo was examined. To assess the capacity of different APC to prime CD4+ T cells, a series of MHC class II I-E transgenic mice that differentially express I-E on APC were utilized. Transgenic mice that express I-E primarily on DC, on macrophages, and on B cells were primed with an I-E restricted peptide in vivo, and the extent of priming was determined by restimulation of CD4+ T cells in vitro with the same Ag. The results indicate that DC are required for priming of CD4+ T cells, and that the extent of priming correlates with the frequency of I-E+ DC. Moreover, DC alone can serve as APC for the peptide Ag, in that priming can be restored in an I-E negative mouse by the transfer of peptide-pulsed I-E+ DC. The potency of DC, compared with B cells and macrophages, to prime naive CD4+ T cells was confirmed with in vitro studies.

L21 ANSWER 29 OF 40 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN

1993:334697 Document No.: PREV199345029422. Peptide and protein antigens require different **antigen presenting cell** types for the priming of CD4-positive T cell in vivo. Constant, S.; Levin, D.; Pasqualini, T.; Flavell, R.; **Bottomly, K.**. Immunobiol. Dep., Yale Univ. Sch. Med., New Haven, CT 06510, USA. Journal of Immunology, (1993) Vol. 150, No. 8 PART 2, pp. 273A.
Meeting Info.: Joint Meeting of the American Association of Immunologists and the Clinical Immunology Society. Denver, Colorado, USA. May 21-25, 1993.
CODEN: JOIMA3. ISSN: 0022-1767. Language: English.

L21 ANSWER 30 OF 40 SCISEARCH COPYRIGHT (c) 2004 The Thomson Corporation. on STN

93:250194 The Genuine Article (R) Number: KX956. PEPTIDE AND PROTEIN ANTIGENS REQUIRE DIFFERENT **ANTIGEN PRESENTING CELL** -TYPES FOR THE PRIMING OF CD4+ T-CELL INVIVO. CONSTANT S (Reprint); LEVIN

D; PASQUALINI T; FLAVELL R; **BOTTOMLY K.** YALE UNIV, SCH MED, DEPT IMMUNOBIOL, NEW HAVEN, CT, 06510. JOURNAL OF IMMUNOLOGY (15 APR 1993) Vol. 150, No. 8, Part 2, pp. A273. ISSN: 0022-1767. Pub. country: USA. Language: ENGLISH.

L21 ANSWER 31 OF 40 MEDLINE on STN DUPLICATE 11
92407320. PubMed ID: 1388189. Activation requirements for CD4+ T cells differing in CD45R expression. Luqman M; **Bottomly K.** (Section of Immunobiology, Yale University School of Medicine, New Haven, CT 06510.) Journal of immunology (Baltimore, Md. : 1950), (1992 Oct 1) 149 (7) 2300-6. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB Murine CD4+ T cells can be subdivided into naive and memory T cells based on surface phenotype, on recall response to Ag, and on differences in activation requirements. Furthermore, several studies have shown that two signals are required for CD4+ T cell activation; one signal is provided by occupancy of the TCR and the other signal is provided by the APC. In this report, analysis of naive and memory CD4 T cells, separated on the basis of CD45 isoform expression, has shown that their requirements for two signals differ. Activation of memory CD4 T cells to proliferate and secrete IL-2/IL-4 only required occupancy of the TCR complex, whereas activation of naive CD4 T cells required an APC-derived signal as well. Moreover, the signal induced by anti-CD3 antibodies differs from the signal provided by anti-V beta cross-linking of the TCR because both antibodies activate memory CD4 T cells but only anti-CD3 activates naive CD4 T cells. Together these data suggest that the consequence of stimulation through the TCR/CD3 signal complex differs between memory and naive CD4 T cells.

L21 ANSWER 32 OF 40 MEDLINE on STN
92164739. PubMed ID: 1347015. Major histocompatibility complex (MHC) control of CD4 T cell subset activation. II. A single peptide induces either humoral or cell-mediated responses in mice of distinct MHC genotype. Murray J S; Pfeiffer C; Madri J; **Bottomly K.** (Section of Immunobiology, Howard Hughes Medical Institute, New Haven, CT.) European journal of immunology, (1992 Feb) 22 (2) 559-65. Journal code: 1273201. ISSN: 0014-2980. Pub. country: GERMANY: Germany, Federal Republic of. Language: English.

AB CD4 T cells activated in vivo in response to human collagen type IV (hCol IV) resemble either T helper type 1 (Th1) or Th2 cells depending on the major histocompatibility complex (MHC) class II genotype of the responding mice. H-2s mice were shown to selectively activate Th1-like cells, releasing interleukin (IL 2 and interferon-gamma in response to hCol IV, whereas H-2b.d mice were shown to selectively activate Th2-like cells, releasing IL 4 and IL 5 in response to hCol IV. These results suggested that MHC class II regulated the type of effector function observed during an immune response. It was of interest to determine if the functional difference observed between the CD4 T cells of the two strains was due to the presentation of different peptides of the hCol IV molecule by the two MHC class II molecules. The present results demonstrate that a single peptide of the collagen IV molecule will elicit a Th1-like response in H-2s strains and Th2-like responses in H-2b.d strains, as was observed when using the intact hCol IV molecule. Furthermore, the failure to generate Th1-like responses in H-2b.d could be overcome by increasing the dose of this peptide in vitro. Compared to H-2s, the Th1-like response in H-2b required 100 times the amount of peptide to reelicit an equivalent response. These data suggest that a single peptide of hCol IV can control the type of effector response observed.

L21 ANSWER 33 OF 40 MEDLINE on STN DUPLICATE 12
92111653. PubMed ID: 1346115. Differential effect of interleukin 1 on naive and memory CD4+ T cells. Luqman M; Greenbaum L; Lu D; **Bottomly K.** (Section of Immunobiology, Yale University School of Medicine, New Haven, CT 06510.) European journal of immunology, (1992 Jan) 22 (1) 95-100. Journal code: 1273201. ISSN: 0014-2980. Pub. country: GERMANY:

Germany, Federal Republic of. Language: English.

AB Freshly derived murine CD4+ T cells are divided into naive and memory cells based on the expression of CD45 isoforms. Cross-linking the T cell receptor CD3 complex either by plastic-bound anti-CD3 antibodies or the antibody presented on non-lymphoid Fc gamma receptor type II-positive Chinese hamster ovary cells in absence of competent **antigen-presenting cells** fails to activate naive cells to either secrete cytokines or to proliferate. In contrast, memory cells secrete their characteristic cytokines [interleukin (IL) 2, IL4, and interferon-gamma] and show significant proliferation to this stimulus. IL 1 however, is required for their optimal clonal expansion. Differential expression of IL 1 receptor mRNA in memory cells also correlate with their responsiveness to IL 1. Thus, these data reveal a basic difference in the requirements for activation of naive and memory CD4+ T cells.

L21 ANSWER 34 OF 40 MEDLINE on STN

90347175. PubMed ID: 1974562. Differences in the expression profiles of CD45RB, Pgp-1, and 3G11 membrane antigens and in the patterns of lymphokine secretion by splenic CD4+ T cells from young and aged mice. Ernst D N; Hobbs M V; Torbett B E; Glasebrook A L; Rehse M A; **Bottomly K**; Hayakawa K; Hardy R R; Weigle W O. (Research Institute of Scripps Clinic, Department of Immunology, La Jolla, CA 92037.) Journal of immunology (Baltimore, Md. : 1950), (1990 Sep 1) 145 (5) 1295-302. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB Previous studies indicate that the 3G11, CD45RB, and Pgp-1 determinants are differentially expressed on CD4+ T cell subsets in the mouse. We used multicolor immunofluorescence staining and flow cytofluorometric analysis to examine the expression of each of these determinants on splenic CD4+ cells from young (age 3 to 6 mo) and aged (age 24 to 26 mo) C57BL/6 mice. The CD4+ pool from aged mice contained significantly reduced numbers of 3G11+ and CD45RBhi cells, but increased numbers of Pgp-1hi cells, in comparison with the young group. Analysis of the simultaneous expression of all three subset determinants on CD4+ cells revealed that, in young mice, the major fraction (greater than 50%) was 3G11+CD45RBhiPgp-1lo. Among the less prevalent cell phenotypes, reductions in 3G11 expression correlated with decreases in CD45RB levels and increases in Pgp-1 levels. The phenotype that dominated the young group (3G11+CD45RBhiPgp-1lo) was approximately fivefold less represented in the aged group. The CD4+ pool from aged mice was characterized by increases in the 3G11-CD45RBvariablePgp-1hi and the 3G11+CD45RBloPgp-1hi phenotypes. To evaluate possible age-associated differences in cytokine secretion patterns by splenic CD4+ cells, purified CD4+ cells from each age group were stimulated in vitro with immobilized anti-CD3 epsilon mAb and accessory cells. At various times thereafter, supernatants from cultures were tested for IL-2 and IL-4 content by using the CTLL.6 and 11.6 bioassays, respectively, and the CD4+ cells were assayed for [3H]TdR uptake. Cell cultures from the aged group exhibited similar peak IL-2 accumulation and lower peak [3H]TdR uptake, but greatly increased peak IL-4 accumulation, as compared with cell cultures from the young group. The expression patterns of subset determinants, in conjunction with cytokine secretion profiles, indicate that, in aged mice, marked alterations occur in the subset composition of the splenic CD4+ cell pool. These findings are discussed in the context of previous findings on changes in T cell reactivity with advancing donor age.

L21 ANSWER 35 OF 40 MEDLINE on STN

89082653. PubMed ID: 2562905. Antigen presentation by B cells. **Bottomly K**; Janeway C A Jr. Nature, (1989 Jan 5) 337 (6202) 24. Journal code: 0410462. ISSN: 0028-0836. Pub. country: ENGLAND: United Kingdom. Language: English.

L21 ANSWER 36 OF 40 MEDLINE on STN

89256662. PubMed ID: 2470817. Monoclonal antibodies to murine CD3 epsilon define distinct epitopes, one of which may interact with CD4 during T cell

activation. Portoles P; Rojo J; Golby A; Bonneville M; Gromkowski S; Greenbaum L; Janeway C A Jr; Murphy D B; **Bottomly K.** (Department of Pathology, Yale University School of Medicine, New Haven, CT 06510.) Journal of immunology (Baltimore, Md. : 1950), (1989 Jun 15) 142 (12) 4169-75. Journal code: 2985117R. ISSN: 0022-1767. Pub. country: United States. Language: English.

AB The TCR is comprised of two variable chains that confer specificity, called alpha:beta or gamma:delta, physically associated with five different molecules that comprise the complex known as CD3. Antibodies to this complex are very useful, as they react with all T lymphocytes. A rat mAb to mouse CD3 has been prepared. It reacts with 100% of T cells in all mouse strains tested but with no other cell type. It binds to the CD3 epsilon chain. This antibody activates cloned T cell lines and normal T cells, provided suitable accessory cells and signals are present. This antibody detects a determinant similar to but not identical with those detected by two previously reported hamster anti-CD3 epsilon antibodies. This antibody fixes C efficiently, and it is thus useful for depletion of T cells from bulk populations. Activation of T cells by one of the three different anti-CD3 epsilon antibodies was inhibited by the Fab fragment of anti-CD4, similar to the effects of anti-CD4 Fab on two previously reported anti-TCR V region antibodies that bind a CD3 epsilon-associated epitope. This further defines a site involving TCR V regions and CD3 epsilon with which CD4 appears to associate during T cell activation.

L21 ANSWER 37 OF 40 CAPLUS COPYRIGHT 2004 ACS on STN

1991:556484 Document No. 115:156484 Immune recognition and effector function in subsets of CD4 T cells. Janeway, Charles A., Jr.; Yagi, Junji; Rojo, Jose; Portoles, Pilar; Carding, Simon; Luqman, Mohammed; **Bottomly, Kim** (Sch. Med., Yale Univ., New Haven, CT, 06510, USA). Proceedings of the International Symposium of the Princess Takamatsu Cancer Research Fund, Volume Date 1988, 19th(Immune Syst. Cancer), 193-208 (English) 1989. CODEN: PPTCBY.

AB A review with 48 refs. The optimal activation of CD4-pos. T-cells involves recognition of peptide fragments presented by class II MHC antigens and accessory signals derived from the **antigen-presenting cells.**

L21 ANSWER 38 OF 40 BIOSIS COPYRIGHT (c) 2004 The Thomson Corporation. on STN DUPLICATE 13

1989:83732 Document No.: PREV198936039823; BR36:39823. **ANTIGEN-PRESENTING CELL** LYSIS ROLE IN IMMUNE RESPONSES AND EFFECT ON QUANTITATIVE ANALYSES OF ANTIGEN PRESENTATION TO T CELLS. JONES B [Reprint author]; HOROWITZ J; KAYE J; KILLAR L; **BOTTOMLY K**; JANEWAY C A JR. SECT IMMUNOL, DEP PATHOL, HOWARD HUGHES MED INST, YALE UNIV SCH MED, NEW HAVEN, CONN 06510, USA. (1988) pp. 291-300. PERNIS, B., S. C. SILVERSTEIN AND H. J. VOGEL (ED.). PROCESSING AND PRESENTATION OF ANTIGENS; P AND S BIOMEDICAL SCIENCES SYMPOSIUM, NEW YORK, NEW YORK, USA, MAY 30-JUNE 1, 1986. XIV+324P. ACADEMIC PRESS, INC.: SAN DIEGO, CALIFORNIA, USA; LONDON, ENGLAND, UK. ILLUS. ISBN: 0-12-551855-2. Language: ENGLISH.

L21 ANSWER 39 OF 40 MEDLINE on STN

90062014. PubMed ID: 2908353. Immune recognition and effector function in subsets of CD4 T cells. Janeway C A Jr; Yagi J; Rojo J; Portoles P; Carding S; Luqman M; **Bottomly K.** (Section of Immunobiology, Howard Hughes Medical Institute, Yale University School of Medicine, New Haven, Connecticut 06510.) Princess Takamatsu symposia, (1988) 19 193-208. Ref: 48. Journal code: 9301172. Pub. country: United States. Language: English.

AB T cells expressing the cell surface differentiation antigen CD4 are involved in most immune responses. Our studies address two issues about CD4 T cell responses to antigen: first, how does the T cell receptor come together with its ligand to generate an immune response, and what is the role of the CD4 molecule in this response? Second, are all CD4 T cells identical in their functional activity, and how does the activating signal

determine the functional outcome of a response? Our studies outlined below suggest that the T cell receptor and its peptide: class II major histocompatibility complex (MHC) molecule ligand come together in a defined orientation determined in part by the binding of CD4 to both the T cell receptor and its ligand. Our studies suggest that the V beta chain is involved directly in MHC antigen recognition, binding self MHC with low affinity and non-self MHC with high affinity. The selective effect of the Mls locus on V beta expression is believed to reflect the binding of the Mls protein directly to the V beta region. CD4 is described as a co-receptor, forming an inducible part of the T cell receptor and binding to the same class II MHC molecule as that receptor. Studies with both cloned lines and normal CD4 T cell populations suggest the existence of two separable subsets with definable function. One set appears to be specialized for the activation of the humoral immune response, while the other drives the cell-mediated immune responses, particularly those involving the activation of macrophages. These two subsets of CD4 T cells have differential activation requirements, seen particularly in the requirement for interleukin 1 (IL-1) in the activation and clonal expansion of CD4 T cells involved in humoral immunity. This requirement for IL-1 may also be observed in the priming of this subset of CD4 T cells. These studies demonstrate that the optimal activation of CD4+ T cells involves recognition of peptide fragments presented by class II MHC molecules and accessory signals derived from the **antigen presenting cells.**

L21 ANSWER 40 OF 40 MEDLINE on STN DUPLICATE 14
86315188. PubMed ID: 2944202. Cell interactions in the immune system: the role of self recognition in the targeting of nonspecific effector molecules by helper T cells. Janeway C A Jr; Tite J P; Horowitz J; Conrad P J; Kaye J; Jones B; **Bottomly K.** Symposium on Fundamental Cancer Research, (1986) 38 45-61. Journal code: 100961284. ISSN: 0190-1214. Pub. country: United States. Language: English.

AB Helper T cells are activated by cross-linking of their receptors by antigen:Ia complexes on the surface of **antigen-presenting cells** and B cells. As a result of this cross-linking, the helper T cell releases several lymphokines that in turn affect the Ia-bearing cell with which the helper T cell is in contact. This interaction is cognate when the effect on the target cell is examined, but it operates by a mechanism that is neither antigen specific nor MHC restricted. Whether the cognate nature of this interaction reflects solely the intimate contact of the T cell with the Ia antigen-bearing cell or whether it reflects a receptor-directed focal release of lymphokines remains to be determined. The molecular basis for functional diversity in helper T cells will have to be determined by examining the factors that regulate lymphokine gene expression in such cells, a process that appears to act at several levels.

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